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Southern Medical Association, Thirty-Fourth Annual Meeting, Louisville, November 12-15, 1940

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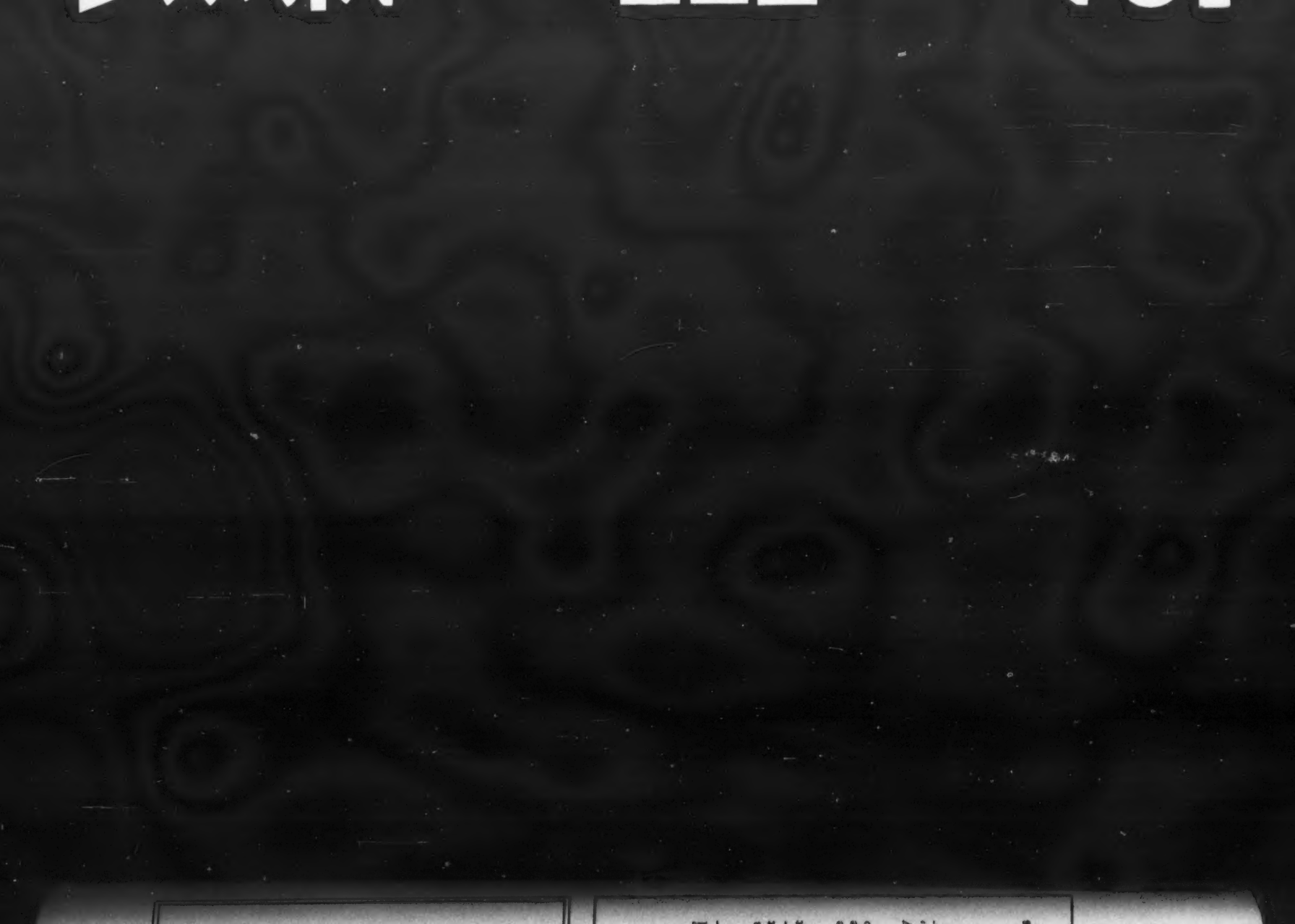

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[1]Rosenheim, M. L.: *Lancet* 2:1083 (Nov. 7) 1936.
[2]Cook, E. N.: *Minnesota Medicine* 20:512 (Aug.) 1937.

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1 *Jr. A.M.A., Dec. 9, 1939, p. 2137.*
2 *Jr. A.M.A., Nov. 4, 1939, p. 1700.*
3 *Sebrell, W. H., Pub. Health Report, Dec. 1939, p. 2121.*
4 *Williams, R. R. and Spies, Tom D., "Vitamin B_1", 1938, p. 132.*

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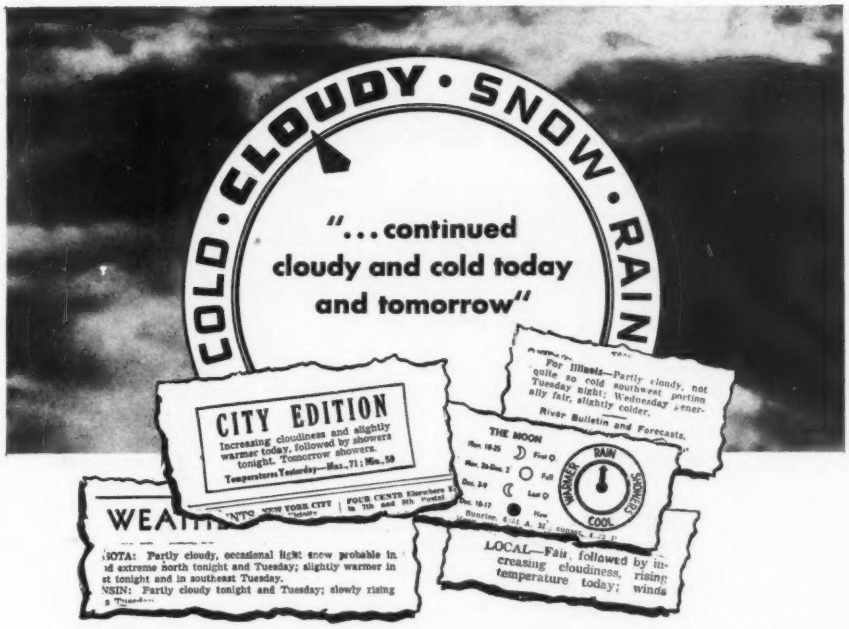
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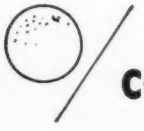

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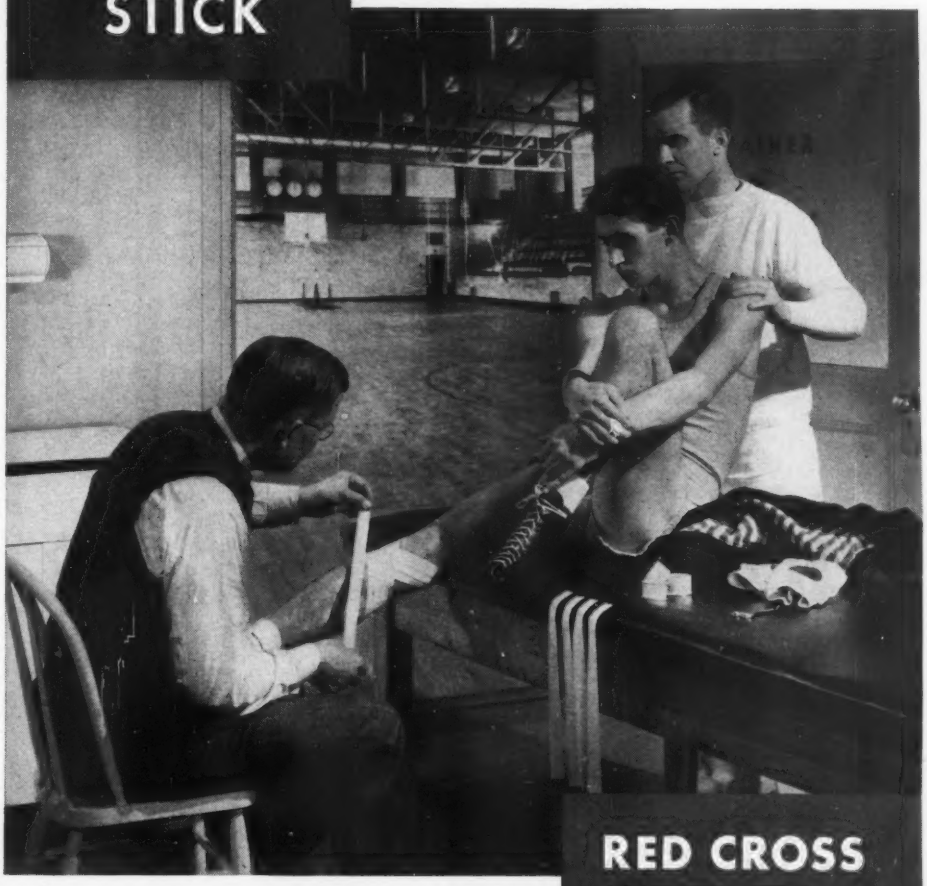

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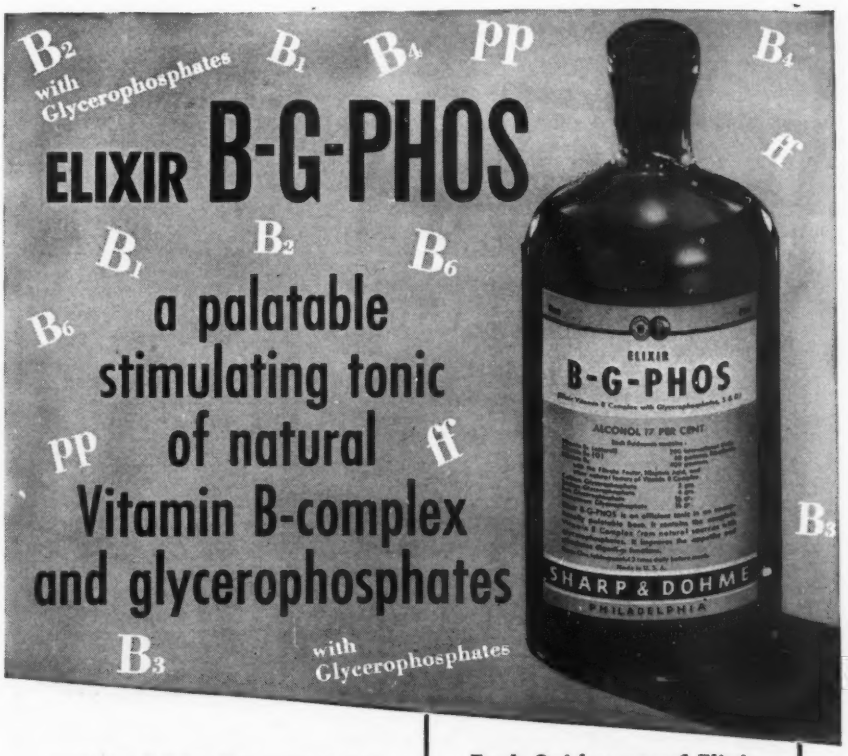

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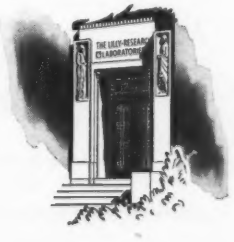

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IRON ALONE					45	40		50
	1		34		51	45		60
	2	1116	50		64	55	48	70
	3	414	68	47	69	66	48	73
	4	−43	77	59	74	71	66	73
	5	+5	79	63	78	72	68	82
	6		80	65	80	75	70	82
	40 Mg. $CuSo_4$ per week		82	67	81		70	82
COPPER ADDED	8		95	77	88	81	75	85
	9		95	85	98	88	82	
	10			85	98		93	

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**Hutchison, J. H., "Role of Copper in Iron Deficiency Anaemia in Infancy", Quarterly Jl. Med. Vol. VII, No. 27, July 1938.*

***Deobald, H. J., and Elvehjem, C. A. (1933) Amer. J. Physiol. 111-118.—Brock, (July 1937) Clin. Sc., 3:1. Also Hemolology Clinic New York Post Graduate Course.*

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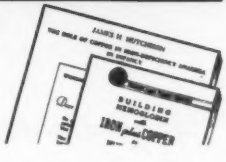

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Constipation . . It is characteristic of most babies fed on milk properly modified with Mellin's Food that they are not troubled with constipation.

Underweight . . Results from the use of properly adjusted Mellin's Food formulas are usually satisfactory, often remarkable, when applied as the daily nourishment for babies who are decidedly underweight.

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You *prescribe* vitamins — but what's the actual intake?

THE PROBLEM is getting the children to take it, getting the Mother to remember *every* day, keeping the dosing going after the interest has dwindled, getting past the first half-bottle and the first week of attention!

Vi-Delta Emulsion tastes like orange syrup and enlists the eager appetite of the children themselves. Mother *lets* them have some if they eat their spinach. They remember it—they plead for it—they prompt Mother at dosing time! The second bottle is sent for and then the third. "Might as well get the larger size." Your little patients *get* the vitamins you prescribe—get them faithfully every day for months! A familiar problem solved!

Vi-Delta Emulsion has as its active principle a concentrate of blended fish liver oils (excluding cod) refined by a new process that really at last disposes of the fish-oil taste which pharmacologists for half a century have so vainly striven to smother or disguise. The concentrate being tasteless, the taste of Vi-Delta Emulsion is simply that of the blended orange juice, sugar and malt which is used as the vehicle.

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"Vi-Delta Emulsion *Lederle*"... 8 oz. and pint bottles—each teaspoonful (4 cc.-5.2 grams) contains 3,200 units U. S. P. XI Vitamin A, when made, and 400 units U. S. P. XI Vitamin D and is equal to minimum strength Cod Liver Oil U. S. P. XI 1939 Supplement.

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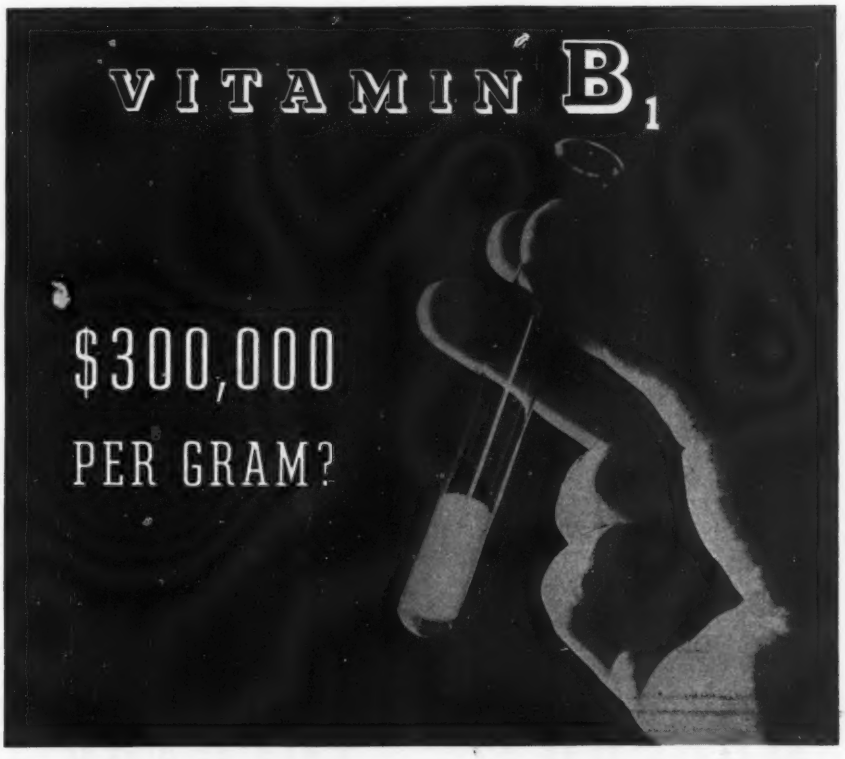

It is considered extremely doubtful whether the isolation, identification, and synthesis of any other substance in the history of biochemistry have required such prolonged and intensive effort as has been expended on vitamin B_1. Conservatively estimated, the first gram of pure vitamin B_1 must have cost an aggregate of several hundred thousand dollars.*

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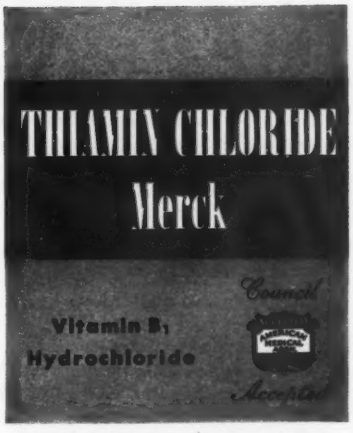
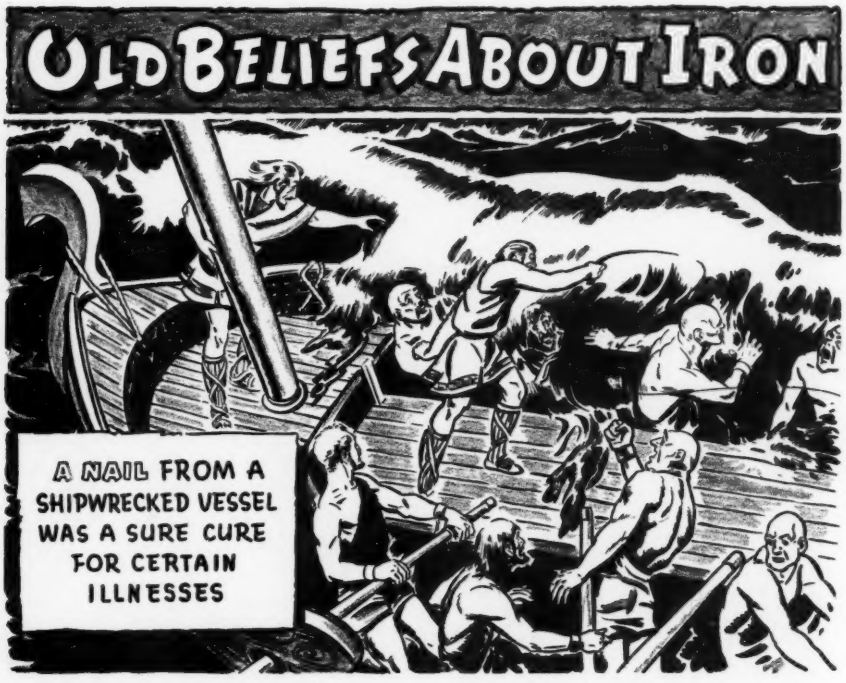


*Williams, R. R., and Spies, T. D., Vitamin B_1 and its use in medicine, p. 138, The Macmillan Co., 1938.

MERCK & CO. Inc. *Manufacturing Chemists* RAHWAY, N. J.



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Mucilose with Kasagra combines 55% of Mucilose (the hemicellulose obtained from the Plantago loeflingii) with 4 minims to the teaspoonful of the tonic laxative, Kasagra.

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Mucilose, by reason of its water-holding properties, exerts a lubricating, softening action in the bowel to produce an easily-passed bulky mass.

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Hemoglobin and Red Cell Count Increase	28%	16%
Hemoglobin Increase	36%	32%
Red Cell Count Increase	56%	40%

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***Archives of Pediatrics, November, 1939.**

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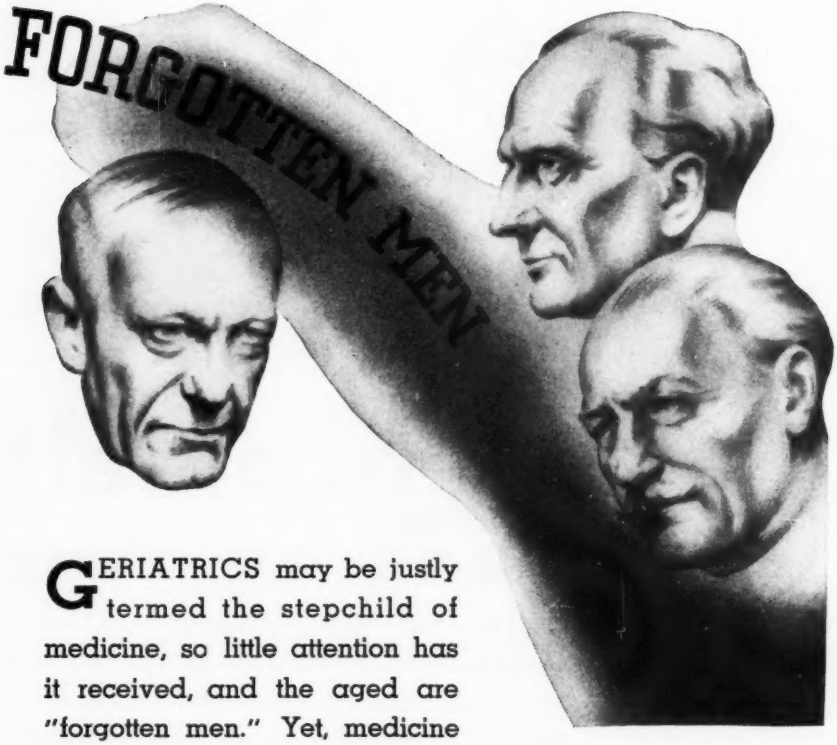

GERIATRICS may be justly termed the stepchild of medicine, so little attention has it received, and the aged are "forgotten men." Yet, medicine can provide much comfort to ease the infirmities of old age, among which constipation is almost ever present. You will find, as many physicians have already found, that Agarol is the preparation well-suited to the treatment of the obstinate constipation of advanced years. The contents of the colon are softened by unabsorbable moisture, evacuation is made easy and painless and devoid of dangerous straining. Such action is, of course, desirable not only in the aged, but in every age group. Agarol is gentle enough for the young child, yet in proper dosage active enough for the adult. ¶ A trial supply of Agarol will be gladly sent to you. It is supplied in bottles of 6, 10 and 16 ounces.

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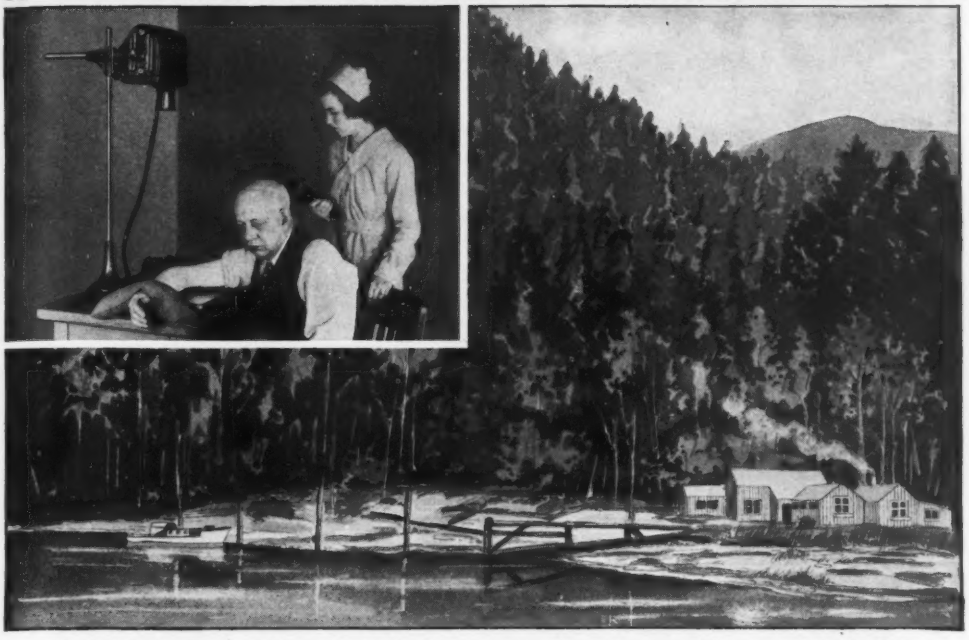

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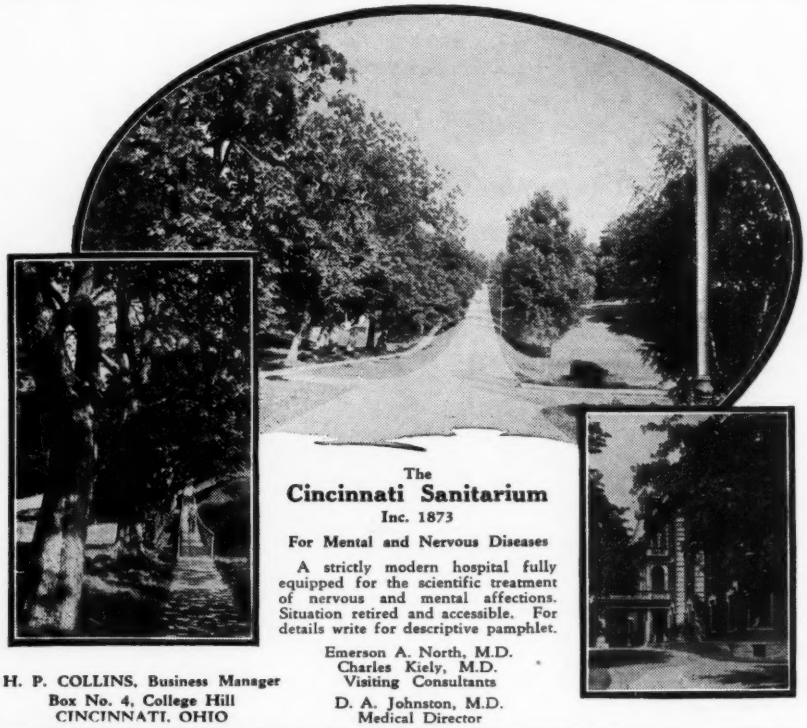

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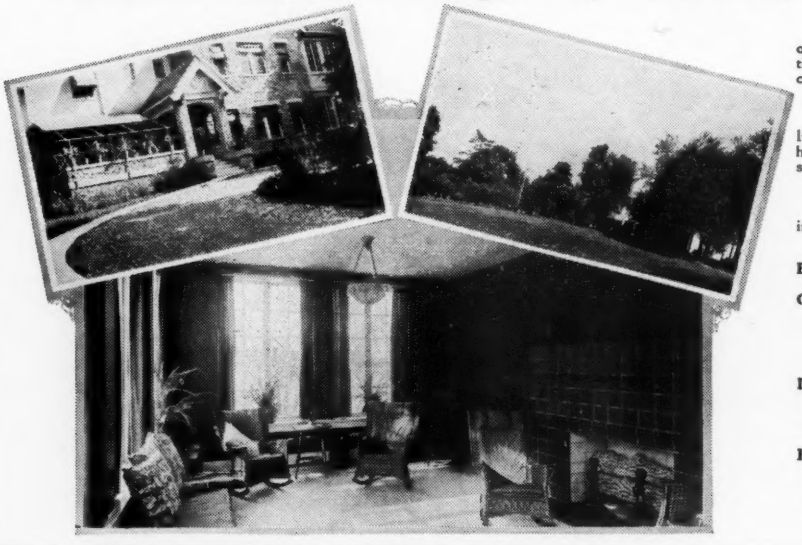

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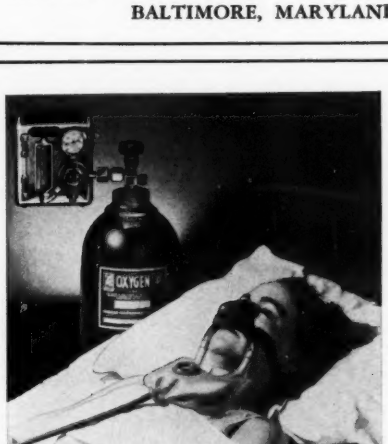

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HYPERPARATHYROIDISM*

By R. M. HOWARD, M.D.
Oklahoma City, Oklahoma

During the past few years more definite knowledge of the physiology of the parathyroid glands has stimulated interest in their pathologic status. For a long time we have recognized hypoparathyroidism which occurred incident to operations for goiter, but ascribed the condition to a lack of the detoxicating influence of the undamaged gland. Not until the work of McCallum and Vogel, in 1913, did we suspect a relationship of the parathyroid glands to calcium metabolism. These investigators found that the blood in cases of tetany contained less calcium than in normal cases, and this explained why the giving of calcium would correct the spasms of parathyroid tetany. Hanson, in 1923, and Collip, in 1924, were able to isolate a physiologically effective extract of the gland. Experimental studies on animals and man soon followed and demonstrated the marked effect on metabolism which followed the introduction of the extract into the body in excessive amounts. It was soon found that parathyroid hormone, when injected into normal individuals, would increase the calcium in the blood, lower the phosphorus, and increase the elimination of both calcium and phosphorus.

The first accurate work on the histology of the parathyroid glands was published by Welch, in 1898, and little has been added to it since then. He described the cells which go to make up the bodies and their arrangement in the gland. In nomenclature only have any of the anatomists since then differed with his description of the component parts of the gland.

Erdheim, in 1903, demonstrated fat granules in the cells and stroma, and showed that their presence depended upon the age of the individual. Kurokawa, after studying a large group of glands from patients of different ages, from that of a seven-month fetus to an individual of 80 years, confirmed this work and further demonstrated that the presence and amount of glycogen depended on age.

The latest work of Castleman and Mallory[1] recognizes four types of cells in the parathyroid gland. The chief cells, the Wasserhelle cells, the pale oxyphil cells and the dark oxyphil cells. They show that the distribution of these cells varies with age, as does the presence of glycogen and fat. They believe that glycogen has something to do with the elaboration of the hormone of the gland, as it is found only in the first two types of cells, which are the cells predominantly noted in early life. Glycogen is not found in the oxyphil cells, which are regarded as involutionary.

The first parathyroid tumor was recognized by DeSanti in 1900. Askanazy[2] first suspected, in 1904, the relationship of decalcification of bone to the parathyroid glands, when he discovered a parathyroid tumor at autopsy in a case of so-called osteitis deformans. While these tumors were thought for several years to have something to do with osteitis fibrosa generalisata of von Recklinghausen, it was not until the removal of one of the tumors in 1925 by Mandl,[3] of Vienna, resulting in the cure of a patient, that general interest was stimulated in hyperparathyroidism. Following this there was a period of confusion during which time surgeons removed, or attempted to remove, parathyroids as remedial measures for various calcium disturbances and their manifestations in the body. Appel and his associates reported in 1928 some 80 cases of parathyroidectomy for ankylosing polyarthritis. This work was followed by Leriche, who also removed normal parathyroids for the same condition. Ballin, of Detroit, reported

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*From the Surgical Department of the University of Oklahoma.

16 cases operated upon for arthritis and later he operated upon cases of Paget's disease and scleroderma on the hypothesis that they were caused by parathyroid over-activity. Improvement was claimed for some of these cases, but accurate metabolic studies do not accompany their reports. Operations were done on a single calcium determination. That this false reasoning should have prevailed is not surprising when we recall the observations of Erdheim, who found parathyroids enlarged in rickets and osteomalacia, and interpreted the parathyroid enlargement as an index of increased parathyroid activity rather than that of an effort of the gland to compensate for a calcium deficiency.

Undoubtedly the bone changes characteristic of hyperparathyroidism have been observed for years. The decalcification and unusual fragility of bones that accompany the condition must have been seen in Greece, and Egypt, and there is evidence that they existed in prehistoric times in the United States. For a long time no distinction was made between the various types of soft bones. While von Recklinghausen is credited with the first accurate description of the disease, many cases were undoubtedly reported previously, and even he confused, and placed in the same class Paget's disease and his so-called osteitis fibrosa.

Following Mandl's original operation in 1925 other authentic cases were soon reported: by Gold, of Vienna, in 1927, Beck of Kiel in 1928, and Sapper and Hunter of Amsterdam in 1929. The first case reported in America was that of Barr in 1929. The second was that of Wilder,[4] also in 1929. Up to October, 1934, Castleman and Mallory reported 160 authentic cases since DeSanti's first case. No doubt there were others that had not reached the literature.

No man or group of men has had many cases. While accurate studies and conclusions have accompanied many of the reports, the work of Churchill[5,6] and his associates in Boston is outstanding, not only because of the number of cases operated upon, but because of the complete studies he and his associates have made in each case.

Their facilities bear out the statement made by Wilder:

"The subject (parathyroid overfunction) involves many fields of medicine and its allied sciences, and thus concerns many groups of specialists. The endocrinologist is faced with a new glandular dysfunction, the biochemist is intrigued by the accompanying abnormalities of the metabolism of calcium and phosphorus, the pathologist and the orthopedist are impressed by the curious disturbances of the skeleton, and the ingenuity of the surgeon is challenged by the difficulties connected with the operative treatment."

Hyperparathyroidism is a condition in which there is an overproduction of the hormone of the gland beyond the body needs. There is evidence that this may occur either as a result of a general hyperplasia of all the parathyroid bodies, or as a result of hyperfunctioning adenomas developing in one or more of the glands. In the latter case Castleman and Mallory, after exhaustive analysis and arguments, conclude that the condition is neoplastic rather than hyperplastic. Churchill classifies diseases of the parathyroid glands into:

(1) Generalized enlargement of the parathyroid glands due to functional hyperplasia, but not associated with hyperparathyroidism (rickets, osteomalacia, pregnancy, nephritis).

(2) Generalized enlargement and hyperplasia of the parathyroid glands associated with hyperparathyroidism.

(3) Focal hyperplasia (adenoma) of one or more parathyroid glands, associated with hyperparathyroidism.

(4) Carcinoma.

The classification, if not entirely in accord with the pathologic findings of Castleman and Mallory, at least is excellent from a clinical standpoint. Its similarity to our present classification in diseases of the thyroid gland is at once apparent. Group one is without surgical interest; group two corresponds to the diffuse toxic cases of goiter; group three to the nodular toxic cases of goiter; and group four is of surgical interest because of known occurrence of carcinoma in the gland. Churchill, in October, 1939, had reported six cases operated upon in group two and fifty cases in group three. He told me in a letter that, strange to say, he had not recently seen a case in group two.

Hyperparathyroidism causes changes in the metabolism of calcium and phosphorus. The body loses its ability to retain these chemicals chiefly in the bones. There is an elevated blood calcium, and an increase in the excretion of calcium in the urine. There is a decreased blood phosphorus and an increase in excretion of phosphorus in the urine. These changes are of diagnostic importance, particularly if the patient is on a low calcium diet, and on repeated determinations the findings are relatively constant, and vary from the normal in either case. The normal for blood calcium is 10 to 12 mg. to 100 c. c.

of blood, the blood phosphorus 3 to 5 mg. to 100 c. c. of blood.

The elevation of the phosphatase in the plasma which has a specific place in the deposition and maintenance of calcium and phosphorus in the tissues, although occurring in other diseases, is of importance when considered in connection with the above studies.

Decalcification of bones is the outstanding clinical manifestation of the disease. Increased elimination of calcium and phosphorus in the urine cause calculi to form, and even calcification of the cortex of the kidney. Progressive impairment of kidney function is frequently seen.

The clinical manifestations of the disease are:

(1) Skeletal changes, generalized decalcification, bone tumors as epulis, or giant cell tumors of bone, fish type vertebral bodies with deformity and shortening of stature; fractures following mild trauma and bone tenderness.

(2) Calcification and disturbed renal function with or without calculi.

(3) Other signs such as polydipsia, polyuria, weakness and loss of strength, constipation, loss of appetite, loss of weight, muscle and joint pains, and frequently anemia with leukopenia.

There is a decreased excitability of the nerves.

On the basis of the above findings, with characteristic changes of calcium and phosphorus in the blood, a diagnosis of the disease entity hyperparathyroidism may be made.

On such a diagnosis operation should be done, and search made for a diffuse involvement of the glands, or the presence of an adenoma in one or more glands. Resection, or removal, is the procedure, bearing in mind that resection may be advisable in either instance in order to preserve sufficient parathyroid tissue for physiologic purposes. Determination of the presence of diffuse general enlargement will require careful judgment. Localization of adenomas may be technically difficult, as parathyroid bodies may be found anywhere from the pharynx to the mediastinum, between the posterior and middle layers of deep cervical fascia, and not always in immediate proximity to the thyroid gland. An understanding of their embryologic development makes this not at all surprising.

The histologic findings in the parathyroid tissue removed in the two types of parathyroid overfunction as described by Churchill are so different that he believes an immediate frozen section would serve to differentiate the two. The hyperplastic type will be formed almost entirely by large Wasserhelle cells resembling hypernephroma, with a greater vascularity, and with absence of fat; while the adenomatous type will show chief cells, larger than normal, at times multinucleated; oxyphil cells as in the normal gland, and at times Wasserhelle cells arranged in alveolar groups.

Churchill says:

"If we are correct in our views, the disclosure of one normal parathyroid should exclude the presence of generalized hyperplasia; similarly the finding of an enlarged gland with the histology of an adenoma should do likewise, although from time to time adenomas will be encountered as tumors of two or more glands. On the other hand, the finding of an enlarged gland presenting the histologic picture of hyperplasia makes an extended search for other hyperplastic glands essential if the patient is to be adequately treated."

The results of operation are immediately striking. Within a few hours the calcium and phosphorus metabolism returns to normal or even below, when tetany may develop. The general symptoms gradually improve. Kidney impairment may to some extent persist, and redeposit of calcium gradually takes place in bone, some weeks or months passing before positive evidence is exhibited by the x-ray. Bone tumors disappear, but the bone cysts formed by fibrous replacement of bone substance persist.[7 8]

Thus we have seen during the past fourteen years the conquering of an old disease and the dramatic addition to our nomenclature of a new clinical entity, hyperparathyroidism.

In 1935, Wilder[4] reported that since the date of the first reported case by Mandl in 1925, he had been able to accept from the literature 135 true cases. There are today probably less than 200 that would conform to his minimal criteria, namely:

"(1) The report of the case has appeared in the literature; (2) that the description of the skeletal abnormality present be consistent with that of generalized osteitis fibrosa, or in the absence of skeletal abnormality, that indisputable abnormality of calcium metabolism characteristic of hyperparathyroidism has been demonstrated by the study of blood and urine; and (3) that a tumorous enlargement, either adenoma or one or more parathyroid glands, or diffuse hypertrophy and hyperplasia of the entire parathyroid apparatus has been found either by operation or micropsy."

To this list I wish to add another, not because one more case is of particular importance, but first because no cases have been reported from our section of the country, and second because I have been able to keep this case under observation for nearly five years since operation.

CASE REPORT

Clarence H. Frye, a white man, aged 20, without occupation, was admitted to Oklahoma State University Hospital January 12, 1935.

He lived at home, had a good outlook, had been unable to work for the preceding three years. There was no family history of tuberculosis, carcinoma, Banti's disease or glandular dysfunction.

His past medical history was essentially negative except for a tonsillectomy in 1931. His chief complaint was of inability to walk without crutches because of deformity and muscular weakness.

He dated the onset of his present illness to 1925, when he was struck in the neck by a blunt object, resulting in a minor injury. Shortly after this he noticed a small lump in the right side of the neck just above the clavicle. Since then the mass had slowly increased in size up to the time of examination. He says that it enlarged on coughing. In 1926, he noticed that his hips were becoming stiff, although he could walk without trouble. In 1929, his thighs gradually bowed outward and he was walking with difficulty. At about this time he noticed a gradual onset of weakness, and when arising from a chair he would have to "climb up on himself." At this time some soreness and pain developed in the muscles and joints. In 1933, his head began to enlarge and he had to buy a larger cap. In 1934, he had trouble raising his arms above his head, and about that time his fingers became clubbed. About one year after the onset of the trouble he had attacks of nausea and vomiting, which lasted for six months. There had been some kyphosis for three years. His weight lately had been about stationary, but his height had been decreasing.

He was a fairly well nourished young man, who walked with a waddling gait aided by crutches. There were several scars on the neck and abdomen. The head was large and prominent in the frontal and parietal regions. The suboccipitofrontal circumference was 24½ inches. His teeth showed evidence of decalcification, but no caries. There was a soft, smooth mass in the anterior part of the neck on the right side just above the clavicle, measuring three inches in diameter. Pressure caused coughing, which bulged the tumor to almost twice its size. The chest was emphysematous in type. There was moderate kyphosis of the spine in the upper thoracic region. The lungs were clear. The heart was normal in size and shape, and there were no murmurs.

There was limited adduction to both shoulder joints and an increased carrying angle of both arms. The fingers were clubbed. There was limited adduction of both hips; the legs were bowed. Other movements were normal. The eyes and ears were normal. There was slight impairment of movement of the right vocal cord.

Blood examination showed red cells 4,480,000; white cells, 7,250; differential normal. Urinalysis showed specific gravity 1,020; albumin 2 plus; occasional white blood cell; Mosenthal normal. Blood chemical examination showed nonprotein nitrogen 35; urea 16; uric acid 1.4; sugar 80; creatinin 1.4; calcium 14.4 to 19 mg.; and phosphorus 4.4 to 2.9 mg.

The Wassermann was negative; examination for Bence-Jones protein was negative; and his basal metabolism was plus 5.

X-ray disclosed a large thick skull with generalized stippling due to absorption of calcium. The suture lines were not closed. There was narrowing of the anterior portion of the bodies of the dorsal vertebrae due to decalcification. There was extreme lack of calcium in the pelvic bones and a 50 per cent decrease in the size of the necks of the right and left femur with upward displacement of the shaft. Large cystic areas involved most of the right ilium. There was extreme deformity of the right and left humerus, cystic degeneration of the left scapula, and lack of calcium in the dorsal and lumbar spine.

The impression was that the condition was osteitis fibrosa cystica with hyperparathyroidism and adenoma of the parathyroid.

Repeated studies of the patient's calcium metabolism were made on a general diet, on a high calcium diet, and on a milk diet in which the calcium content of the milk was determined in the laboratory.

Fig. 1

Gross specimen of parathyroid adenoma removed February 1, 1935. The gross specimen, as shown above, consisted of an ovoid, moderately soft, semifluctuant, reddish gray mass 9 cm. in greatest diameter, with a moderately smooth surface apparently covered by a thin capsule. The cut surface revealed a cystic cavity (match in the specimen separates the cut surfaces to show the cavity) about 6 cm. in diameter, containing clear watery fluid. The inner surfaces are somewhat uneven or trabeculated, red, soft and more or less smooth and glistening.

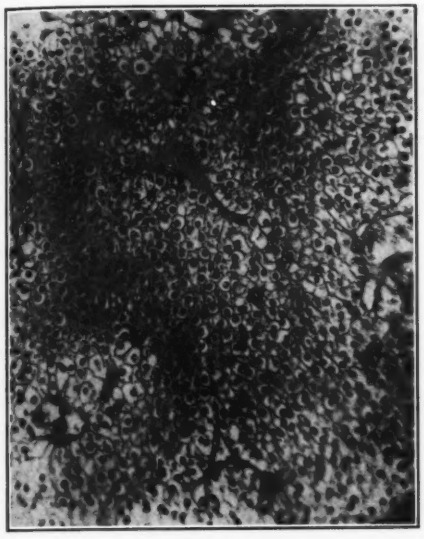

Fig. 2

The above is a high-power microscopic field showing the columns of cells occurring in a manner to form more or less distinct lobules. Blood vessels are moderately numerous and reticulum scanty. The characteristic clear cells ("water-clear cells"), with ballooned cytoplasms, predominate. The pathologic diagnosis is adenoma of the parathyroid, transition Wasserhelle type.

He was operated upon on February 1, 1935, under local and nitrous oxide anesthesia. A large cystic tumor was removed from the right side of the neck. This was three inches in diameter, dark in color, and was loosely attached to the posterior surface of the right lobe of the thyroid gland. There were dense adhesions and many large blood vessels on the posterior surface. The tumor was three-fourths intrathoracic, but was removed without difficulty. The pathologist's report was adenoma of the parathyroid, transition Wasserhelle type. The wound was closed with small rubber tube drainage.

Postoperatively he was given 2,000 c. c. of normal salt subcutaneously. His blood calcium three hours later was 15.3 mg. Six hours postoperatively it was 10 mg. Nine hours postoperatively it was 10.2 mg.

At this time calcium gluconate grains 30 was given intravenously and repeated every three hours during the night. The next morning at 7:00 o'clock the blood calcium was 19.1 mg. The calcium gluconate was discontinued, and in six hours the blood calcium was 10 mg. He received no more calcium, he had no signs of tetany and made an uninterrupted recovery. He remained in the hospital for three weeks, during which time repeated determinations of calcium were made, which were always within normal limits.

We have fortunately been able to keep this man under observation during almost five years since he was operated upon.

On leaving the hospital March 1, 1935, his blood calcium was 10.2 mg.; blood phosphorus 3.8; albumin in urine plus 2. On June 13, 1935, the blood calcium was 10.3 mg.; blood phosphorus 3.6 mg.; albumin plus 2. He felt much stronger and walked without crutches. X-ray at this time failed to show any appreciable change in the bones. On September 15, 1935, blood calcium was 10.4 mg.; blood phosphorus 3.8 mg.; albumin in urine plus 2. X-ray showed an apparent increase in the calcium in all the bones. The old cystic areas were less prominent.

He returned in June, 1936; April, 1937; September, 1938, and September, 1939. On each occasion the blood calcium and blood phosphorus were normal. He continued to run 2 plus albumin in the urine, and x-ray showed evidence of increasing calcification of bone, although the bone cysts had persisted. He has gradually resumed activity, and on his last visit stated that he had been driving a truck for the previous year. He had during this time been entirely well and felt that he had entirely regained his normal strength. His deformity is permanent, but gives him little inconvenience.

Since I reported this case in 1935, our staff has been somewhat parathyroid conscious. During this time, 31,761 cases have been admitted to our institution, only fifteen of which have been suspected of having hyperparathyroidism, and not one of which proved to be a true case.

SUMMARY

(1) A brief discussion is presented of hyperparathyroidism.

(2) Because of lack of time, the etiology of the condition has not been considered.

(3) Definite requirements essential to a diagnosis of hyperparathyroidism are discussed.

(4) A typical case of parathyroid adenoma with hyperparathyroidism operated upon and kept under observation for nearly five years, with complete relief of symptoms, is submitted.

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PARATHYROID OSTEOSIS*

REPORT OF A SEVERE CASE WITH SUCCESSFUL REMOVAL OF A LARGE PARATHYROID TUMOR

By JAMES VANCE, M.D., F.A.C.S.
JACOB ROGDE, M.D.
and
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In 1904, Askanazy first believed that there was a relation between osteitis fibrosa cystica and the parathyroids, and in 1907 Erdheim advanced the theory that osteitis fibrosa cystica produced tumors of the parathyroid glands. Mandel, of Vienna, in 1925, conclusively proved that parathyroid tumors cause osteitis fibrosa cystica rather than the reverse and in that year he brought about improvement in the symptoms of a patient suffering with this disease by the removal of the parathyroid glands. Since that time his work has been repeatedly confirmed by others.

Tumors of the parathyroid glands, usually benign adenomas, give rise to symptoms of the condition known as hyperparathyroidism, which may or may not include bone symptoms. Characteristically, in about 60 per cent of cases, bone disease is found and this is given the descriptive name of parathyroid osteosis. It must be understood that the osseous condition, while important, is only a part of the disease. There are two quite distinct types of bone changes which may be found independently or may be found together in the same case. In one there is a generalized granular osteoporosis and in the other there are multiple bone cysts.

CLASSIFICATION

In the classification of hyperparathyroidism there are three chief groups of symptoms which may be found separately or together. The first type is that with bone involvement. The second shows renal involvement and here, as in the osseous group, there are two types of symptoms. In one there are renal calculi, and in the other, signs and symptoms of renal insufficiency, caused by the calcinosis. There is a third group of rare types of hyperparathyroid disease. One of these consists of hyperparathyroidism simulated or complicated by osteitis deformans.[18] In another there is no bone involvement, but an associated tumor of the pituitary gland is present which some men believe produces the parathyroid tumor.[19,22] Albright has described a syndrome with skin pigmentation and sexual precocity in females which is definitely a symptom of hyperparathyroidism.[12] This rare group serves greatly to complicate the picture of hyperparathyroidism, but fortunately the large majority of cases fall into the more or less classical and readily recognized groups.

There is no satisfactory explanation of the etiology of hyperparathyroidism. Lack of vitamin D has been considered a factor, largely because the majority of cases have been reported from the New England states. The case which we are reporting does not strengthen this view, for the patient has had an adequate supply of sunlight all her life, living outdoors a good deal and in an area of the Southwest which is richest in sunshine of any section of the United States. Race apparently has very little to do with the condition, because cases have been reported from most parts of Europe, the United States, and in a Chinese.[31]

PATHOLOGY

The pathologic changes found in the parathyroid glands vary somewhat. The isolated adenoma is the commonest finding and easiest to recognize, and it may ordinarily be removed surgically. Unquestionably there are cases which show a generalized hyperplasia of all the parathyroid glands and these cases are difficult to diagnose and treat. Ewing believes that from the micropathologic standpoint it is very difficult to tell hyperplasia from adenoma. Most of the tumors show all the cellular elements, although either the principal or oxyphil cell may predominate and the hormone may be produced by all the cells in all probability.[38] Experiments have shown that parathyroid hormone is approximately twice as concentrated in the abnormal gland as it is in the normal one.[30] It is believed that only about 60 per cent of enlargements of the parathyroid gland give recognizable symptoms.

The changes in the bones from a pathologic standpoint are not typical of anything and show absorption of bone chiefly. Most of this destruction is in the form of a lacunar absorption with some accompanying attempt at regeneration of bone visible microscopically. In the large bone cysts there is a hollow cavity with a lining.

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Some authors have suggested that large bone cysts are a more advanced stage of the generalized osteoporotic form, but this is probably not correct.[27]

SYMPTOMS

The symptoms caused by hyperparathyroidism may be divided into different categories, depending on the system affected. Symptoms due to changes in the skeletal system are very pronounced only when a pathologic fracture occurs. This occurs rather commonly and is often the thing which first brings the patient to the physician. Deep aching in the bones is present in some cases. The symptoms due to hypercalcemia are malaise, constipation, loss of appetite, gastro-intestinal disturbances, foot strain and weakness. The increased amount of calcium in the urine is a rather common cause of symptoms and produces polyuria, polydipsia, and later leads to the production of kidney stones and renal colic or gravel in the urine.

X-rays in these cases are usually quite characteristic. There is a granular osteoporosis which typically involves most of the bones of the body and is especially marked in the skull. In addition to this, one may see multiple bone cysts of varying size. Sometimes the osteoporosis is absent and only the multiple cysts are present. Usually these cysts are disseminated rather widely over the body and they are sometimes difficult to differentiate from simple bone cysts, since the latter may also be multiple.

Chemical studies to determine the calcium, phosphorus and phosphatase content of the blood are very valuable. The calcium is markedly elevated, the phosphorus moderately decreased and the phosphatase moderately elevated. The blood calcium is elevated because the excessive amount of parathyroid hormone causes decalcification of bones and calcium goes into the blood stream. Phosphatase is an enzyme important in the regeneration of bone. It is found to be elevated in parathyroid osteosis because nature makes an attempt to form new bone where the old bone is being removed. It is interesting to note that the amount of phosphatase is greatly elevated in osteitis deformans, because here the predominating change is a proliferative one with new bone formation.

The differential diagnosis in a typical case of parathyroid osteosis is usually not difficult to make because of the typical x-rays and the blood chemical findings. The chief conditions to be differentiated are: osteitis deformans, osteomalacia, senile osteoporosis, osteogenesis imperfecta, solitary cysts, giant cell tumor, multiple myeloma, and metastatic malignancy.

TREATMENT

The most effective treatment is removal of the parathyroid tumor. The tumor is usually palpable and if so can be removed surgically fairly easily. If a mass is not palpable and the diagnosis seems certain, it is often wise to explore the neck and search for a tumor. Sometimes a generalized hyperplasia is present instead of a simple tumor and in these cases it is much more difficult to decide exactly what to do. Many men recommend the excision of most of the parathyroid glands, leaving a little parathyroid tissue. Probably less than 100 parathyroid tumors have been successfully treated surgically because of the difficulty of finding the tumor and the rarity of the disease. X-ray treatment has been suggested as an alternative to surgery, but its value is somewhat questionable. Cutler[14] has reported good results with this method, but does not advocate its general use. It has been suggested that it may be used advantageously in cases where surgery is contraindicated. In cases of generalized hyperplasia of the glands it gives the poorest results and this is where one would most like to use x-ray therapy. It has been conclusively shown that x-rays have no effect on normal parathyroid glands experimentally[13] and this may be the reason that irradiation is not always beneficial clinically.

The prognosis in cases of parathyroid disease varies. Following the removal of the tumor, death may occur because of the sudden withdrawal of a hormone to which the body tolerance is very high. Other causes of death are nutritional edema with vomiting, kidney damage, anemia, dehydration, and weakness. In general, the prognosis is good in an early case and becomes worse as the case advances.

CASE REPORT

The case which we wish to report is a woman, aged 47, married, white, and a resident of Alpine, Texas. She was referred to us by her local physician because of fractures of both femurs which she had sustained about five weeks previously. Her past history revealed that she married at the age of 29 and had three pregnancies with toxemia during each pregnancy. There were two stillbirths and one normal child. The onset of her illness was difficult to determine. She was a Christian Scientist and unwilling to discuss it. She had not seen a physician for her present illness until the time of her fractures, five weeks before she was seen by us. With some difficulty the history of the onset of weakness and pains in the legs between fifteen and

twenty years before was obtained. These symptoms had continued; she thought she had arthritis and paid little attention to them. She became worse year after year until six or seven years before we saw her, at which time her stomach began to bother her. Weakness and gastro-intestinal upsets continued with increasing severity and she lost a great deal of weight. She kept going from bad to worse with extreme weakness, nausea and vomiting, muscle aching all over, slight polyuria, and inability to walk, all of which she had when she was first seen by us.

Fig. 1
Tumor in the neck before removal.

A B

Fig. 2
(A) Right femur in June, 1939. (B) Right femur in September, 1939, three months after removal of parathyroid tumor.

On examination she presented a pitiable picture of a woman with severe emaciation and weakness, resenting any attempt to move her or examine her and moaning with pain. She was in a short body cast to protect the fractures of her femurs. Examination of her neck showed a small walnut sized tumor which was situated opposite the lower pole of the thyroid on the left side. This tumor had first been noticed a little over two years before her admission, and she said had been of about the same size since that time. Examination of her legs revealed a very wide spread between them, due apparently to a coxa vara. X-rays revealed fractures of both femurs in about the middle. These fractures were transverse in type and showed practically no displacement, but a moderate amount of angulation. The x-rays of her pelvis showed a marked granular osteoporosis of the entire pelvis with the necks of the femurs almost gone, there remaining only a small pencil-like piece of bone connecting the head to the trochanter on either side. The skull showed typical osteoporosis, as did an x-ray of one humerus. In the right femur there was an area of destruction which resembled a cyst, although it was not well defined nor was the absorption complete within the cyst. Chemical examination of her blood revealed the calcium to be 13.8 milligrams, phosphorus 2 milligrams, and the phosphatase 21 Bodansky units.

It was apparent that the patient needed treatment for two things. The parathyroid tumor should be removed, the position of the fractures should be improved, and a comfortable bilateral long leg hip spica applied. Accordingly, two days after admission the patient was given rectal anesthesia with tribromethyl alcohol reinforced with intratracheal cyclopropane, and the parathyroid tumor was carefully dissected out. It was found to be encapsulated and was removed from the region of the left inferior portion of the thyroid gland. It was relatively round in shape and measured 1½ inches by 1¼ inches by 1¼ inches. It weighed 17 grams and was removed without undue difficulty. While it was being removed the cast which the patient had on was taken off, and the femurs manipulated into as good position as possible. A bilateral long leg spica cast was applied.

Dr. George Turner, of El Paso, made a pathological diagnosis of parathyroid adenoma on the tumor. A portion of the tumor was sent to Dr. Ferdinand Helwig, of St. Luke's Hospital, in Kansas City, Missouri, who confirmed this opinion and made a diagnosis of "glandular and cystic type of chief cell adenoma of the parathyroid gland with transitions from chief to pale oxyphile cell types."

The patient stood the operation very well and her immediate post-operative course was good. However, on the fourth day she began to vomit and feel somewhat ill. The following day she developed evidence of tetany in the form of a characteristic spasm of the

fingers and hands. Administration of intravenous calcium was immediately begun in small amounts, but the patient rapidly became worse and developed a full blown tetany. The dose of calcium was greatly increased until she was getting 10 c. c. of 20 per cent calcium gluconate every two hours intravenously, making 24 grams in 24 hours. Giving the huge doses of calcium helped the patient's tetany somewhat, but did not relieve it completely, and parathyroid hormone therapy was begun during the third day of the tetany. One c. c. of parathyroid extract (100 units) was given every eight hours and this was continued for four days. The tetany promptly stopped and the parathyroid hormone was discontinued.

Fig. 3
X-ray of the pelvis showing generalized osteoporosis and absorption of the femoral necks.

Fig. 4
Photograph of tumor. Size in inches.

After two and one-half weeks the amount of calcium gluconate given was cut in half and at the end of another month it was again reduced 50 per cent to 6 grams in 24 hours. At the end of two and one-half months, intravenous calcium was discontinued entirely. Six weeks following the operation 6 grams of calcium gluconate a day by mouth was begun and is still being given. When the administration of a large amount of calcium was instituted immediately after the operation the patient improved rapidly. She vomited for 4 or 5 days, but by the end of three weeks was feeling well and able to eat with a better appetite than she had had for months. Chemical studies of her blood 2 days postoperatively showed the calcium to be 9 milligrams, phosphorus 2.22 milligrams, and phosphatase 19 Bodansky units. One month after her operation the calcium was 8.5 milligrams, phosphorus 1.53 milligrams, and phosphatase 7 units. In order to keep the blood calcium level anywhere near normal it was found necessary to give the large doses of calcium gluconate intravenously, described above.

Five weeks after her operation she was in good enough condition to send her back to her home, where she was placed under the care of her former physician. Fourteen weeks after her original operation she returned for a check-up and was found to be in much better condition generally. She had gained weight, felt very well, and had no complaints whatever except those relative to the fact that she was in a cast. The cast was removed and x-rays showed the right femur to be moderately well united. The left femur showed some union, but not very much, and there was slight motion at the fracture site. Since the fracture appeared to be healing well, it was decided to reapply a cast to allow further time for union to occur. At that time, fourteen weeks postoperatively, her blood calcium was eleven milligrams and her phosphorus 4.1 milligrams. Originally this patient's blood test for syphilis was negative and her red and white blood counts and hemoglobin were within normal limits. Four weeks after her operation her hemoglobin had dropped to 60 per cent and her red blood count to 3,200,000, and this was unquestionably due to the large amount of intravenous calcium which she was given at that time. Liver and stomach extract with iron were started and at the time of her check-up examination, fourteen weeks postoperatively, her condition seemed to be excellent in every way, and her red blood count and hemoglobin were again normal.

COMMENT

There are several interesting features of this case. The size of the gland is of particular

interest, because it was a very large tumor. There have been reported at least four successfully removed tumors larger than ours. Another interesting thing is the very extensive bone changes found in this patient. These with the fact that the patient was in very poor condition when she was operated upon makes it interesting that she stood the operation well and ultimately recovered. Probably the administration of a very large amount of intravenous calcium was largely responsible for her recovery. Twenty-four grams of intravenous calcium gluconate a day would seem to be a very large amount, but our patient tolerated it well. However, even with this large amount of calcium it was necessary to give parathyroid hormone for a short time to relieve the tetany. The diagnosis in this case was quite easy to make, for the bone changes, tumor in the neck, and blood calcium, phosphorus, and phosphatase values were all quite typical.

If the patient's fractures of the femurs heal well and her bones recalcify so that she may try walking, it will be most interesting to see how well she is able to walk with her femoral necks almost entirely gone and the upper end of the trochanters riding against the pelvis. It is possible that these trochanters riding against the pelvis will sustain the weight of this small woman. If they do not, the question comes up as to whether a bilateral Shanz osteotomy or some other operative procedure on the hips may ultimately be indicated.

In a relatively isolated community such as ours we do not expect to see a case of this kind often, or to have the good fortune successfully to remove a tumor as large as this from a very ill patient.

SUMMARY

The subject of hyperparathyroidism in general is discussed and the literature briefly reviewed.

A case of severe parathyroid osteosis is presented in which there were extreme granular osteoporosis, fractures of the middle of both femurs, and almost complete absorption of both femoral necks.

A parathyroid adenoma measuring 1½ by 1¼ by 1¼ inches and weighing 17 grams was removed.

Following removal of the tumor the patient had a somewhat stormy convalescence and it was necessary to give 24 grams of calcium gluconate intravenously a day to maintain anything like a normal blood calcium level.

The patient ultimately made a satisfactory recovery. She has been observed for 5 months and her fractures are uniting and her bones slowly recalcifying.

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DISCUSSION (*Abstract*)

Dr. Ralph K. Ghormley, Rochester, Minn.—Dr. Breck is to be congratulated on the excellent presentation he has made of the apparently typical case of parathyroid tumor associated with parathyroid osteosis, and for bringing again to our attention this rather unusual clinical picture which we should be able to recognize.

In 1932, I attended a medical meeting at which a whole day was given over to discussion of parathyroid tumors. During the course of that day, almost every disease of bones imaginable was discussed as a possible result of parathyroid disturbance of one sort or another. From that time on, the interest in the condition has certainly decreased, probably because of the fact that those who have been writing on the subject have sifted the matter down to a very limited group of cases, and there we stand. While other bone conditions may be due to parathyroid tumors, the fact remains that one cannot demonstrate it. This may be due in some instances to the remote situation of the tumor, like that in a case reported from the Massachusetts General Hospital in which three exploratory operations of the neck were made and no tumor found. Finally an exploration of the mediastinum revealed a tumor and its removal caused improvement. There are some cases from the roentgenographic standpoint alone and indeed from the clinical standpoint, too, disregarding the laboratory findings, which border pretty closely on this condition; that is, you see evidence in roentgenograms that are very much like it, yet you cannot establish the picture of a parathyroid tumor without other findings already noted. I myself have way back in my mind an idea that some day some more of these cases will be shown to be due to parathyroid disturbances of one type or another. Yet I have not any right to make this statement now.

I certainly would not want to subscribe to any effort to treat these patients by removal of the parathyroid without demonstrable lesions of the parathyroid gland. So far as I know, there is no case of satisfactory proven relief by roentgen treatment of the parathyroid gland.

Dr. Paul C. Colonna, Oklahoma City, Okla.—This whole subject of parathyroid over-activity has been increasingly brought into the foreground during the past few years. The interest is evident by the number of articles that are constantly appearing in the literature on the subject. In the *Quarterly Cumulative Index Medicus* during the six months period January to June, 1939, there were 67 articles relating to the parathyroid glands.

This paper of Dr. Breck focuses our attention on the amazing effect that its hyperactivity has upon the bony structures of the body, and he has reported to us a most interesting case with to date a most satisfactory result. I mention "to date" advisedly, for I should like to recall to you that the first case recorded in the literature of the removal of an adenoma for osteitis fibrosa cystica was reported by Mandle, of Vienna, in 1926. His patient was bedridden and two months after the removal of the adenoma he reported the patient able to walk. Five years later, however, this patient was again admitted to the hospital on account of recurrence of her original symptoms with progressive deformity of the osseous system. She was re-operated upon, no tumor was found, and a total thyroidectomy was done. Examination of the removed thyroid showed two normal parathyroids and Mandle reports that the patient subsequently showed no improvement. As this and subsequent reports accumulate in the literature we shall be doubtless able to obtain a clear-cut idea of the permanency of cure following removal of the parathyroid adenomata, but the difficulties of the subject are complex and many.

From a technical standpoint, a localized swelling about the region of the thyroid, accompanied by clinical evidence of an adenoma of the parathyroid as in the author's case, indicates the surgical removal of this tumor. This does not, however, in any way guarantee that we have removed the entire cause of the generalized disease, for we know that normally these four little glands are frequently found in atypical locations and that more than one adenoma may be present. Adenoma has been found behind the mediastinum, and the surgeon said it was necessary to resect a portion of the manubrium in order to obtain sufficient exposure for its removal. Even the removal of a normally placed parathyroid adenoma is considered quite difficult, and in addition to these technical difficulties there is the added danger of removing too much of the affected parathyroid tissue. Lahey says that in his thyroidectomy operations he routinely has the thyroid searched for parathyroid tissue, and if this is present, he reimplants the normal parathyroids into the left sternomastoid muscle, for the danger of removing all of these small but potential power houses leads to the death of the individual. In view of these surgical difficulties, several authors have recommended irradiation of the neck area following surgery in the hope of treating not only the obvious adenomata, but those of aberrant location.

The clinical picture of the pathologic state of these glands is becoming increasingly distinct and we know that at least three conditions may result from over-activity: first, osteitis fibrosa cystica of von Recklinghausen; second, the osteoporosis case which only occasionally will show cystic formation; and third, certain types of renal disease. Rankin some time ago laid down the following diagnostic criteria for over-activity of

these glands: first, a prolonged history of skeletal pain and weakness; second, definite roentgenologic evidence of bony decalcification often with osteitis fibrosa cystica; third, a normal or elevated amount of blood calcium with an increased excretion of calcium, giving rise to a negative calcium balance; fourth, a normal or elevated blood phosphorus with an increased excretion of phosphorus, giving rise to a negative phosphorus balance, and to these should be added an elevated blood phosphatase, for this indicates the degree of bone involvement.

Dr. Frank L. Fort, Jacksonville, Fla.—A patient of mine of this type, a 13-year-old girl admitted to the hospital with widespread infectious arthritis, had not bone cysts. She had been in bed for several months. X-ray had shown consistently for several months marked osteoporosis. She had fever and pus and blood in the urine, and finally a urologic consultation revealed three stones in both kidneys. Blood chemical examinations showed a high calcium, that never was over 12, but never under 10 mg. per 100 c. c. of blood, and her phosphorus was low. This is the typical picture that is not seen in any other condition that I know except hyperparathyroidism. She was in such poor general condition, with both kidneys involved with a bad infection, that surgery was impossible, and we sent her out to the convalescent home, where she had a high caloric diet, including concentrated vitamins and sunshine, in the attempt to build her up for an operation.

She eventually got well without any treatment whatsoever. As I look back on the case, I am strongly of the opinion that she had a dietary deficiency disease that probably upset her endocrine balance, with seemingly an over-active parathyroid.

We have had two other cases that were borderline that I do not feel nearly so confident were parathyroid cases. One of them, besides her kidney infection, bad tonsils, hookworm and anemia and living in very destitute circumstances, was, of course, a serious problem, but she recovered with no further treatment than removing the tonsils, treating the hookworm and feeding her.

Dr. W. K. West, Oklahoma City, Okla.—I should like to call your attention to a case reported yesterday afternoon by Dr. R. M. Howard,* of Oklahoma City, Chairman of the Section on Surgery for this meeting. Dr. Howard's patient was a boy of 19 who came in on my service not only with hips somewhat similar to these, but also shoulders and the spine and the skull. He was operated upon by Dr. Howard six years ago, and in seven months there was remarkable improvement in the bone structure, especially of the spine and of the skull. This patient reported back about a month or two ago, six years after operation. Nothing had been done from the standpoint of correction of bone deformities and he had rather marked bowing of the femur. But he is now well and fat and making his living driving a truck, and evidently no further bone change is taking place.

Dr. Frederick A. Jostes, St. Louis, Mo.—I had occasion to see one of the very first patients treated for this condition in Europe in 1924, a young New York woman who was then in the clinic of Dr. Rollier in Leysin, who had this disease and was sent to Vienna to have her parathyroids removed. She had had all sorts of operations before this time. Her recovery offered a very striking example of what this rather simple procedure would do for such an individual.

We have had a number of these cases in St. Louis, one of which was particularly striking to me because the disease of hyperparathyroidism accompanied an acute poliomyelitis. The patient had the entire picture of hyperparathyroidism, including a kidney involvement, all of which cleared up and was immediately relieved when he had his parathyroids removed.

Dr. Guy W. Leadbetter, Washington, D. C.—I have never seen a case of hyperparathyroidism with an adenoma. However, I have seen several cases which were considered to be hyperparathyroidism. They were proven only in so far as they showed blood chemical changes, elevated calcium and diminished phosphorus, and x-ray evidence. One case was a lady of 59 who reached for the strap of her car to leave the car and fractured her clavicle. In the x-ray we found a cystic condition and following up that evidence, we x-rayed the ribs and the humeri. They both showed granulocytic osteoporosis. We feel, therefore, that with her blood findings she had a hyperplastic type of hypothyroidism. Exploration was not deemed advisable. There was no evidence of tumor. Accordingly, she was treated with x-ray over the neck only. The fracture, of course, healed promptly; most of them do. The cyst in the clavicle completely disappeared.

She also had a cyst in the distal phalanx of her fourth finger on one hand which cleared up. The calcium remained at about the level of 13 mg. and the phosphorus reached 3.

Another lady had a rather generalized osteoporosis of the granulocytic type with a great deal of pain. Her skull was involved, the arms, the pelvis and the legs. She was likewise treated with x-ray. She showed essentially the same findings and because of her age (she was well over 60) the bone showed very little return to normal. Strange to say, her pain disappeared.

There is a great deal of aberrant parathyroid tissue through the body. It has been found in the mediastinum. It has been found in the female breast. It has been found in the pelvis. Consequently, if we remove hyperplastic parathyroid in the neck and get no results, it may be because there is hyperplasia elsewhere, and if we utilize the x-ray in the neck alone and get no result, we still may have a hyperplasia elsewhere in the body. I think that x-ray therapy in this condition is worth investigating.

Lacking the evidence of an adenoma, removal of parathyroid tissue is always dangerous.

Dr. Breck (closing).—Most of the cases in which a subsequent relapse occurs are either those in which there is a hyperplasia and in which not enough parathyroid tissue has been removed, or, as Dr. Leadbetter suggested, those in which there is some as yet undetermined factor. The point is very well taken that the ultimate outcome of this case is far from established.

The etiology, as we have said before, is unknown. Dr. Leadbetter's idea about hyperplastic parathyroids

*Hyperparathyroidism: SOUTHERN MEDICAL JOURNAL, this issue, page 123.

elsewhere in the body is an excellent one in connection with the treatment.

It is impossible to explain the matter of a transitory case which appears to be a definite hyperparathyroidism, but which apparently clears up. For some time there was a popular theory that vitamin D had something to do with the production of this disease, largely, I think, because the greatest number of cases have been reported in areas where there is the least sun. However, our case certainly opposes that theory, because she comes from the sunniest part of the United States; it is even sunnier than Florida. She was reared in West Texas and took sun baths all her life.

I did not stress the fact that the fractures healed well. It seems amazing that a woman with so little calcium in her bones and two fractures of the femurs should grow a lot of bone across both fractures.

RADIATION THERAPY IN CARCINOMA OF THE FUNDUS OF THE UTERUS*

By CHARLES L. MARTIN, E.E., M.D., F.A.C.R.
Dallas, Texas

The attitude of surgeons towards radiation therapy in cancer of the uterine fundus ten years ago was summarized by Stacy[1] who wrote:

"Radium and roentgen rays have been used at the Mayo Clinic for only a small number of patients who were poor surgical risks and results have been poor. If radium is used in amounts sufficient to destroy the carcinoma, ulceration of the healthy endometrium occurs and the mucosa of the bladder may be affected also."

However, this attitude has slowly changed. Heyman[2] reported that results obtained with radiation alone were as good as those accredited to surgery in 1927, and similar encouraging reports have since been made by Healy and Cutler,[3] Norris,[4] Neill,[5] Arneson,[6] Ward and Sackett[7] and others.

Although many gynecologists still oppose its use, radiation therapy has slowly established itself as a valuable addition to and often a complete substitute for surgery and there are several very good reasons for this trend. Most patients suffering from carcinoma of the corpus are beyond middle age and many of them are afflicted with other diseases which make them very poor surgical risks. In a series of 333 cases reported by Stacy only 10.5 per cent were less than forty-five years of age and many were well along in years. Obesity, cardiorenal disease and cardiovascular disease were encountered with surprising frequency and Scheffey and Thudium[8] diagnosed diabetes in 10.2 per cent of the patients coming under their observation. A total hysterectomy is a radical procedure and even when the cases are carefully selected the operative mortality varies from 5 to 8 per cent in different clinics. Heyman[9] recently reported 100 of 224 cases studied at the Radiumhemmet in Stockholm as technically operable but physically unsuited for surgery and gave this finding as his chief reason for seeking a safer method of treatment.

Experienced surgeons are willing to admit that operation offers little when the malignant tumor shows a high degree of cellular undifferentiation under the microscope. Mahle[10] in a report from the Mayo Clinic made sixteen years ago observed that not a single case falling in his group IV obtained a cure following hysterectomy. However, good results were obtained in 50 per cent of a series of similar cases with radiation by Healy and Cutler and most observers now believe that surgery has no place in the treatment of grade IV (histologic) neoplasms of the uterus.

Sampson,[11] who admits that he has had little experience with radium, objects to its use without surgery because he feels that extension of carcinoma beyond the confines of the uterine wall cannot be detected unless the abdomen be opened. If the detection of such extensions made any great difference in the plan of treatment Sampson's contention should be seriously considered but the author has been able to find only an occasional case report claiming good results from surgical intervention following this complication. In fact, in many instances the procedure is harmful and Scheffey and Thudium conclude that radiation alone and in some instances radiation followed at a later date by operation produce the best end results when extension has passed beyond the uterine wall. Healy and Brown produced a 10 per cent five-year salvage in a small group of these patients in this manner. Fortunately corpus carcinoma grows slowly and extra-uterine manifestations of the disease are encountered infrequently. For this reason Scheffey and Thudium found external extensions in only 13.2 per cent of their cases. It seems reasonable to assume that a total hysterectomy should produce a cure when all visible and palpable evidence of the disease is limited to the uterus and adnexa but statistics fail to bear out this assumption. Stacy's figures show that 61 per cent of 103 cases dying of cancer after a hysterectomy had local recurrences at the site of operation, and we are forced to the conclusion

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*Chairman's Address, Section on Radiology, Southern Medical Association, Thirty-Third Annual Meeting, Memphis, Tennessee, November 21-24, 1939.

that operability cannot always be accurately determined even when the abdomen is opened.

Sampson also contends with considerable justification that intra-uterine radium applications are often of little value because complicating lesions or the shape of the uterine cavity prevent the approximation of the ordinary radium container to the malignant lesion. The complicating conditions mentioned are submucous fibroids and intra-uterine polyps but fortunately both of these complications are rare. In Stacy's series polyps were present in 10 per cent and uterine fibroids in 37 per cent of 333 cases of corpus carcinoma but the incidence of submucous fibroids is not given. Since this type of fibroid is relatively uncommon it seems fair to assume that its occurrence in the series was low. Such a lesion may completely mask a carcinoma arising in the endometrium so that it cannot be reached with a curette. For this reason uteri containing large submucous fibroids should always be regarded with suspicion, especially when hemorrhage does not respond to a castration dose of radiation.

A radium capsule may be placed in contact with a malignant growth in the fundus of a small uterus with relative ease but the blind placing of one or more capsules in a large uterine cavity of uncertain shape presents a difficult problem which has been recognized by radiologists for many years. Healy and Brown[12] have been much impressed with the importance of the size of the organ as a prognostic factor and state that their results with a straight tandem applicator have been poor in all cases having an enlargement exceeding in size a two and one-half months' gestation. Experience has shown that adenocarcinoma of the uterus of all histologic grades will respond to adequate doses of radiation and for this reason the expenditure of considerable effort in the preparation of proper applicators seems justified.

In 1930, Brown[13] described his plan of using three intra-uterine radium capsules attached to long slender metal rods which extend outside of the vagina. The central rod is rigid, but capsules are attached to the ends of the other two by sections of clock spring. With these applicators,

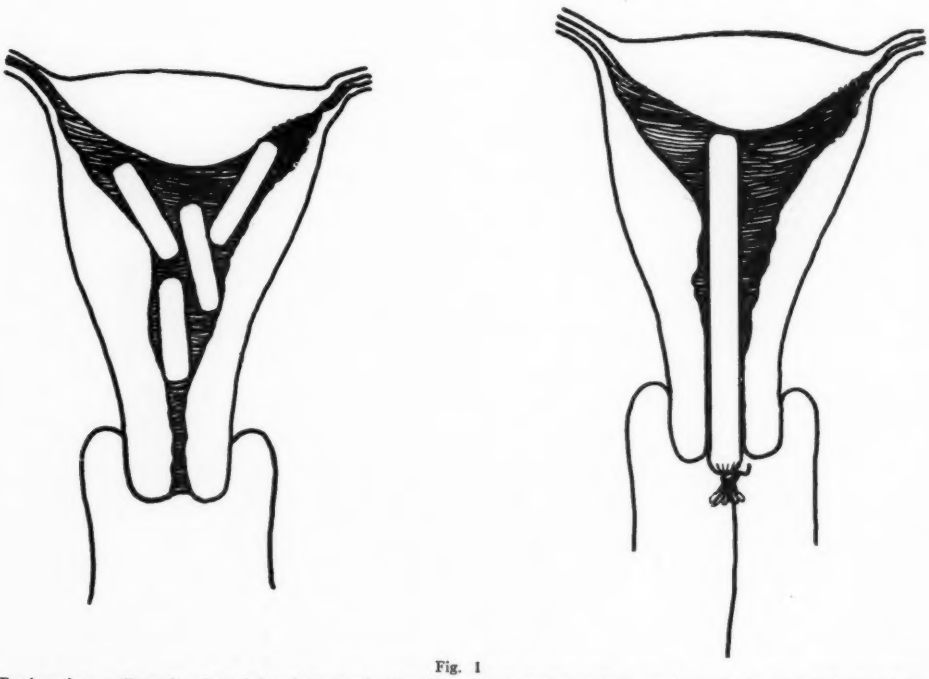

Fig. 1

Tracings from radiographs of an injected uterus showing that a single tandem radium capsule may be placed well away from a carcinoma in one horn of the organ and multiple loose capsules may work down into the cervical canal so as to prevent drainage.

one capsule can be placed in the center of the fundus while the other two are forced into the horns of the uterus with the aid of the elastic springs. When these capsules are in place the rods are clamped within a large metal tube in the vagina by means of a set screw and thereby secured in position for considerable periods of time. This scheme not only provides radiation in both uterine horns, but it allows free drainage through the cervix at the same time. Since carcinoma frequently begins in one of the horns and spreads over the upper portion of the fundus, any efficient method must place radium in these regions.

Bowing and Fricke[14] have attempted to fix one or two radium capsules in various portions of the cavity by attaching them to a stiff wire. The suspicious areas are treated by shifting this single applicator from one position to another at intervals. Schmitz and Schmitz[15] have prepared a more complicated device consisting of three radium capsules hinged at a central point to form a Y. When one of these capsules is placed in the cervical canal the other two pass into the horns of the uterus. After they are inserted they can be swung apart by a screw protruding from the cervix. In 1936, Heyman recommended that the uterus be filled with small heavily filtered radium capsules attached to threads in an effort to radiate evenly the entire organ. The number required usually varies from eight to twelve. Radium is also applied in the vagina to prevent metastases in this region.

Interstitial technics have shown a steady trend towards the use of small units of radium well distributed for long periods of time because larger doses can be given in this way and the normal tissues show less damage. Heyman's small capsule plan shows a similar trend and in 1935 we adopted a modification of his method for enlarged uteri. We have since attempted to improve the procedure and at present our fundus technic is carried out as follows:

When the organ is normal in size, capsules containing 50 or 75 mgs. of radium in 25 mg. units placed in tandem are inserted into the uterine cavity. The capsule walls are made of platinum 1.0 mm. thick, covered with a layer of aluminum measuring 1.0 mm. in thickness. The radium is contained in short steel needles each of which measures 1.5 cm. in length and holds 6.25 mgs. They are placed in the capsules in groups of four. A capsule is selected which reaches from the cervical canal to the top of the fundus and a total dose of 3,000 to 4,000 mg. hours is given in a period of three days. This method is similar to that recommended by Healy and Brown.[16] When the uterus is enlarged the size, shape and depth of the cavity are first estimated with a probe. Each horn is then curetted separately and the tissue from each side is examined in an effort to determine the location of the tumor. In the beginning several radiographs of malignant uteri injected with skiodan and acacia were studied so that the exact shapes of the cavities might be mapped out. This practice has been discontinued because of the danger of disseminating cancer cells into the peritoneal cavity, but the work done showed conclusively that even in uteri of moderate size, single capsules could not be brought in close proximity with carcinomatous tissue situated well out in one of the horns.

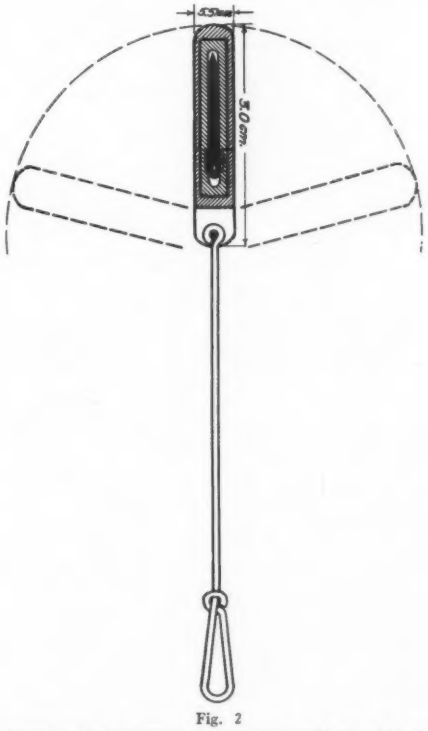

Fig. 2

Drawing showing a new intra-uterine applicator with the radium capsule cut in half. This capsule contains a 6.25 mg. radium needle surrounded by 1.0 mm. of platinum and a thin aluminum outer shell. The outer aluminum capsule is hinged to a soft wire so that it will rotate through an arc of 180 degrees in one plane only.

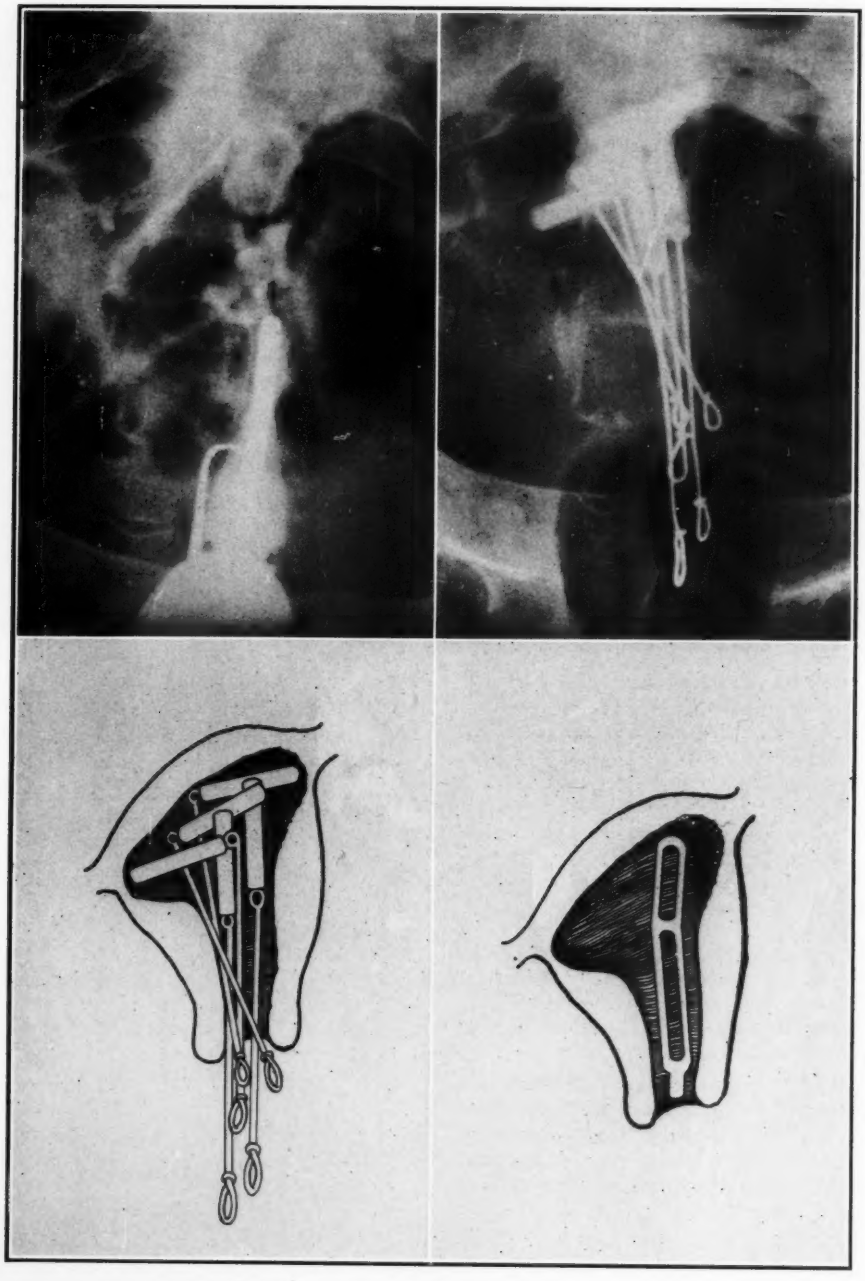

Fig. 3

Radiographs showing an actual uterine cavity containing adenocarcinoma in the left horn visualized by a thin coating of hippuran after the injection of carbon dioxide, before and after the insertion of five hinged radium capsules. The drawings below show a tracing of the multiple capsules in place, and a subsequent treatment with a single tandem capsule which is bent slightly at the upper end.

During 1935 and 1936 we attempted to fill the uterus with small lead capsules having a wall thickness of 1.0 mm. Each capsule was made just large enough to contain a 6.25 mg. steel radium needle having a length of 1.5 cm. and a diameter of 1.5 mm. A thread was attached and the container was wrapped in a single layer of self-vulcanizing rubber. After the uterine cavity was filled with these small capsules the vagina was packed with sterile gauze. This method yielded some very good end results, but it had one distinct disadvantage. Periods of radiation of four or five days were necessary for the administration of effective doses and drainage was often blocked by the loose capsules, at least one of which usually slipped down into the cervical canal. As a result a temperature elevation frequently occurred on the second or third day and it was found necessary in several instances to interrupt the treatment to alleviate this complication.

Our experience indicated the need for a small well filtered capsule applicator which could be placed at any angle in the upper uterine cavity and held there without interfering with the drainage of secretions through the cervical canal. The applicator illustrated in *Fig. 2* was finally devised in 1936. An aluminum capsule measuring 3.0 cm. in length is hinged at one end to a piece of soft wire having a length of 6.5 cm. A loop at the lower end of the wire indicates the plane of rotation of the capsule on its hinge so that the applicator can easily be guided into either uterine horn or around an obstruction. The aluminum capsule contains an inner platinum capsule having a wall thickness of 1.0 mm. and a cavity just large enough to receive a 6.25 mg. steel radium needle having a length of 1.5 cm. In most instances five or six of these containers can be placed in intimate contact with the involved portion of the uterine cavity. The looped ends of the wires protrude through the external os and are held in place by gauze packs soaked in a mixture of balsam peru and castor oil. The wires hold the capsules well up against the top of the fundus and maintain excellent drainage through the cervical canal. Since the capsules rotate only in one plane, they can be introduced into a cavity of any shape, even though it forms an acute angle with the cervical canal. These applicators remain in place for five days, but the packs are changed every second day. The total dose given in this way amounts to 3,750 to 4,500 mg. hours. Since carcinoma of the fundus frequently extends downward toward the cervix, this treatment is augmented by a twenty-four-hour application of the 75 mg. tandem capsule placed in the cervical canal and lower uterus. The large total dose of 5,550 to 6,300 mg. hours is well tolerated when given in

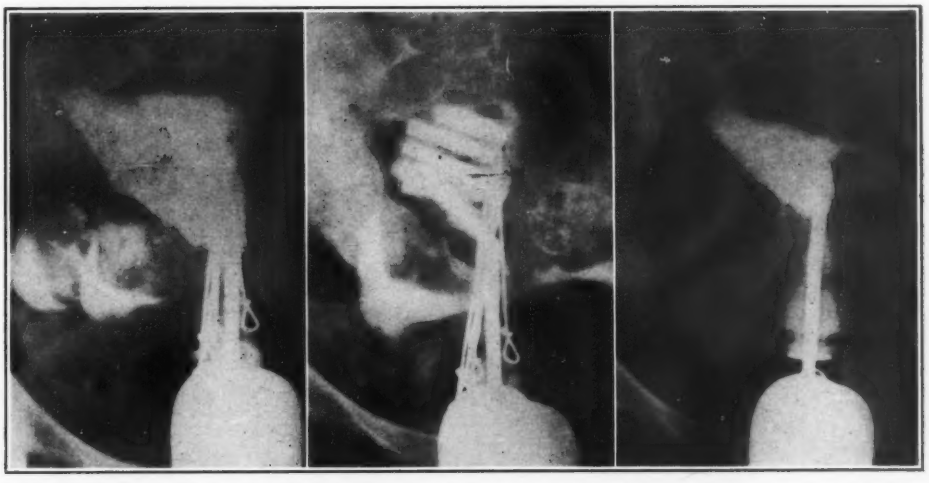

Fig. 4

Radiographs of a large uterus with adenocarcinoma, Grade II, in an elongated right horn before and four months after radium therapy. A dose of 4,500 mg. hours was given with the six hinged applicators placed as shown in the central radiograph and a dose of 1,800 mg. hours was then added with a single capsule of the type shown in Fig. 3. A curettage was negative for carcinoma when the last radiograph was made.

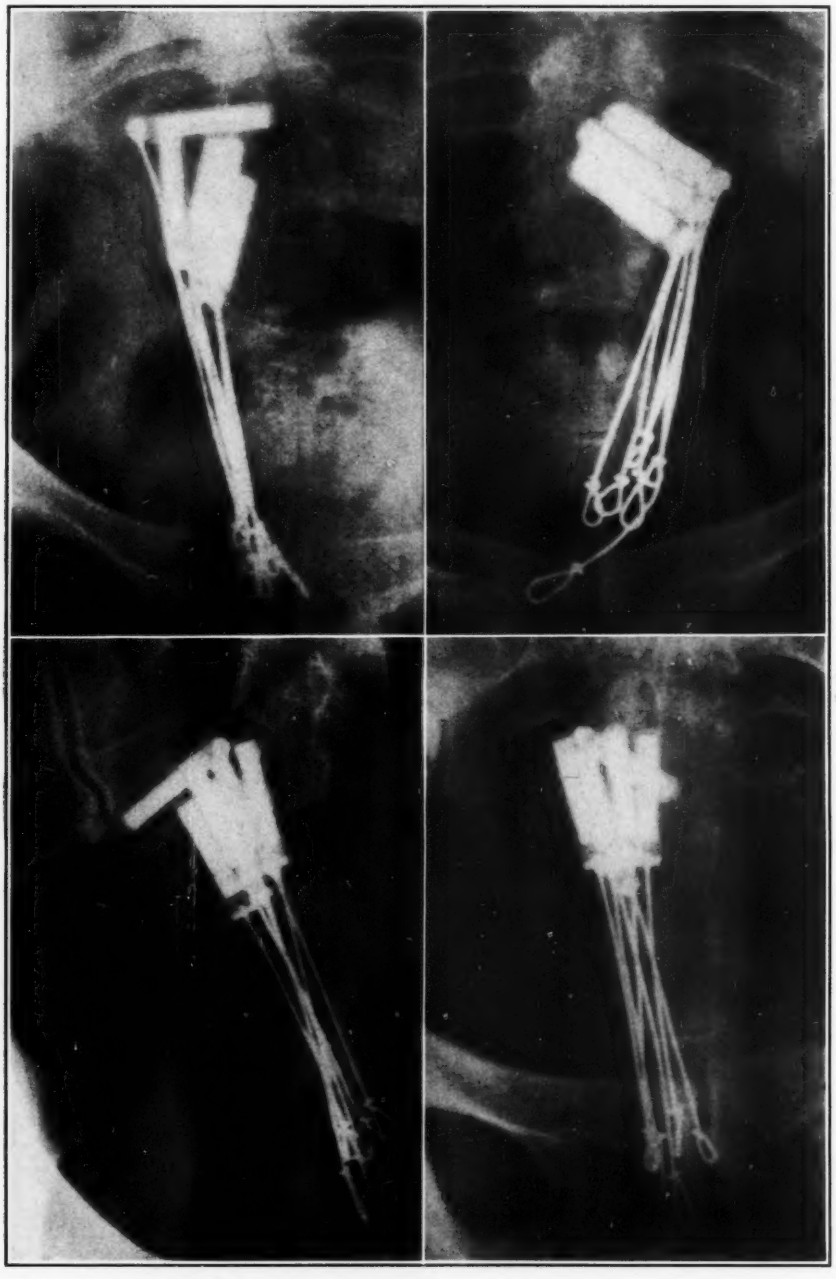

Fig. 5

Radiographs of the hinged capsules placed in four different cases of carcinoma of the fundus of the uterus. When possible, at least one capsule is placed transversely in the top of the uterine cavity. Excellent drainage was obtained in each instance.

Table 1

FUNDUS CARCINOMA TREATED DURING PAST FIVE YEARS

	Age	Size of Uterus	Pathology	Radiation Therapy		Curettage After Radiation	Hysterectomy	Results
				Radium	X-Ray			
1 Mrs. J. W.	58	Normal	Adenoca. II	75 mg. 20 hr. / 50 mg. 18 hr. } 2400 mg. hr.	600 r x 4	Negative	None	Symptom-free 4 yr. 6 mo.
2 Mrs. R. S.	45	1½ x normal	Adenoca. II	5 lead caps. 66 hr. / 50 mg. cap. 20 hr. } 3062 mg. hr.	600 r x 4	Negative	At 2 mos.	Symptom-free 4 yr. 5 mo.
3 Mrs. F. L. M.	60	Normal	Adenoca. III	4 lead caps. 72 hr. / 50 mg. cap. 24 hr. } 3000 mg. hr.	600 r x 4	Negative	None	Symptom-free 4 yr.
4 Mrs. W. E. Mc.	61	2 x normal	Adenoca. I	5 lead caps. 96 hr. / 5 wire caps. 120 hr. } 3000 mg. hr.	600 r x 4	Negative	None	Symptom-free 3 yr. 11 mo.
5 Mrs. V. R.	59	3 x normal	Adenoca. I	6 lead caps. 96 hr. / 50 mg. cap. 24 hr. } 4800 mg. hr.	.....	Positive	At 3 mos.	Symptom-free 3 yr. 11 mo.
6 Mrs. P. C. S.	51	Normal	Adenoca. I	4 lead caps. 120 hr. / 50 mg. cap. 19 hr. } 3950 mg. hr.	.....	Negative	None	Symptom-free 3 yr. 10 mo.
7 Mrs. H. S. H.	54	Normal	Adenoca. I	2 wire caps. 18 hr. / 50 mg. cap. 48 hr. / 50 mg. cap. 24 hr. } 3825 mg. hr.	.....	Negative	None	Slight discharge at 2 yr. 11 mo.
8 Mrs. M. K.	56	1½ x normal	Adenoca. I	50 mg. cap. 48 hr. / 50 mg. cap. 24 hr. } 4200 mg. hr.	250 r x 13	Negative	At 4 mos.	Died after 2 yrs.
9 Mrs. C. G.	52	2½ x normal	Adenoca. II	6 wire caps. 120 hr. 4500 mg. hr.	400 r x 7	Negative	None	Died after 2 yrs.
10 Mrs. M. M.	68	2 x normal	Adenoca. II	5 wire caps. 132 hr. 5137.5 mg. hr.	.....	Not done	None	Alive with recurrence 1 yr. 11 mo.
11 Mrs. J. E. S.	59	4 x normal	Adenoca. I	6 wire caps. 96 hr. / 75 mg. cap. 24 hr. } 5400 mg. hr.	600 r x 4	Negative	None	Alive with recurrence 1 yr. 8 mo.
12 Mrs. W. D. D.	72	1½ x normal	Adenoca. II	5 wire caps. 96 hr. / 50 mg. cap. 21 hr. } 4050 mg. hr.	.....	Negative	None	Symptom-free 1 yr. 6 mo.
13 Mrs. W. B. F.	54	3 x normal	Adenoca. II	5 wire caps. 96 hr. / 75 mg. cap. 20 hr. } 4500 mg. hr.	.....	Negative	None	Symptom-free 1 yr. 2 mo.
14 Miss L. H.	54	Normal	Adenoca. I	50 mg. cap. 24 hr. / 50 mg. cap. 36 hr. } 3000 mg. hr.	.....	Negative	None	Symptom-free 1 yr.
15 Mrs. S. C.	51	2 x normal	Adenoca. II	6 wire caps. 120 hr. 4500 mg. hr.	600 r x 4	Negative	4 mos. later	Symptom-free 9 mo.
16 Mrs. L. T.	50	Normal	Adenoca. II	50 mg. cap. 48 hr. / 50 mg. cap. 19 hr. } 3350 mg. hr.	600 r x 4	Negative	None	Symptom-free 8 mo.
17 Mrs. W. A. Mc.	61	1½ x normal	Adenoca. II	6 wire caps. 96 hr. / 50 mg. cap. 24 hr. } 4200 mg. hr.	600 r x 4	Negative	None	? Abdom. recurrence at 7 mo.
18 Mrs. W. P. P.	73	3 x normal	Adenoca. III	6 wire caps. 120 hr. / 75 mg. cap. 24 hr. } 6300 mg. hr.	600 r x 4	Negative	None	Symptom-free 6 mo.
19 Mrs. F. R.	59	3 x normal	Adenoca. II	6 wire caps. 120 hr. / 62.5 mg. cap. 26 hr. } 6125 mg. hr.	.....	Negative	None	Symptom-free 4 mo.
20 Mrs. E. G.	60	2 x normal	Adenoca. II	6 wire caps. 120 hr. / 62.5 mg. cap. 26 hr. } 6125 mg. hr.	.....	Negative	None	Symptom-free 4 mo.

this manner and the results obtained in a relatively small group of cases are very encouraging. Some of these patients have received single doses of deep x-rays (600 r) administered to four 15 cm. portals laid out over the front and back of the pelvis so as to cross fire the uterus. The factors are 200 kv., a filter of 0.75 mm. of copper and 1.0 mm. of aluminum, 25 ma., and a target skin distance of 50 cm. In a few instances the multiple divided dose method advocated by Healy[17] has been used, but we feel that the radium technic constitutes the important part of the procedure.

At the end of six to eight weeks a second curettage is done. If malignant tissue is obtained a hysterectomy is advised provided the risk is not too great. If no cancer tissue can be obtained with a curette the patient is told that her chances are somewhat better with operation than without it and surgery is advised if no contraindications exist. Many patients elect to disregard this advice.

The estimation of the relative value of radiation therapy and surgery is very difficult because the clinical classifications used by different authors vary and as a rule all of the favorable cases are treated surgically while the doubtful and complicated cases receive radiation. When large groups of statistics are averaged the five-year salvage accredited to hysterectomy alone amounts to roughly 50 per cent of the patients operated upon. Heyman states that in a group of 85 clinically operable cases treated with radiation and operated upon only when radiation failed, the five-year salvage was 55 per cent. It is interesting to note that when he applied this same technic in a series of 224 patients in all stages of the disease 43.7 per cent survived the five-year period. Norris and Dunne[18] salvaged 47.8 per cent of 115 cases by operation, but used preoperative radiation in many instances. However, they report 43.8 per cent of 89 cases alive five years when only radiation was used. Healy and Brown used preoperative radiation in a series of 189 patients and removed the uterus when the risk was not too great. In this group 39 per cent of 96 cases treated with radiation alone and 55 per cent of 93 cases treated with both radiation and surgery survived the five-year period. When the difference in the material treated is considered it must be admitted that radiation has made a very creditable showing, and refinements in technic may produce even better figures in the future.

Since our present technic has not been in use for five years, no statistics of any great value are available. However, the figures presented in *Table 1*, which cover 20 consecutive cases of all types treated during the past five years, are of some interest. A good primary result evidenced by a negative curettage, the disappearance of symptoms and no recurrence during the varying periods of observation was obtained in 15 of the 20 patients and six cases have remained symptom-free for more than three years. A hysterectomy was done after the radiation therapy was completed in four instances. Three of these operations were done in our own hospital and residual carcinoma was found in only one of the uteri removed. No report on the uterus removed elsewhere could be obtained.

SUMMARY

A radiation technic is recommended for carcinoma of the fundus of the uterus as the primary procedure in all cases. When the organ is normal in size and shape, a tandem radium applicator is used with a dosage of 3,000 to 4,000 mg. hours. When the uterus is enlarged the lower segment receives 1,800 mg. hours given with a tandem applicator. This is augmented by 3,750 to 4,500 mg. hours given with five or six small radium capsules attached to long wires by hinges and applied directly to the affected portion of the uterine cavity. X-ray therapy is added at times, but is not considered essential. If a curettage done six weeks after radiation obtains malignant tissue, operation is advised when the risk is not too great and the histological grading is less than IV.

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DISCUSSION (*Abstract*)

Dr. Franklin B. Bogart, Chattanooga, Tenn.—Almost two years ago I visited Dr. Martin's clinic in Dallas and heard him talk to a small group about some of his methods of treating carcinoma of the fundus. For a year and one-half I have used capsules made according to his model, and I have found the method very satisfactory.

Obviously, in a short period of time, with the small group of cases that I have treated by this method, I am not able to report any statistical results, but I have found the procedure extremely useful, and I think it is a valuable addition to the mode of treating carcinoma of the fundus.

Dr. Harold G. F. Edwards, Shreveport, La.—About twenty years ago, when the question of the treatment of carcinoma of the cervix was brought up at a medical meeting, there was considerable controversy and argument. Now one rarely hears discussion of whether surgery or irradiation should be used in the treatment of carcinoma of the cervix.

Gradually, as we have improved our methods of irradiation, we have seen an increase in the number of five-year cures following irradiation.

Seven years ago, in our tumor clinic group, we began by treating all of our cases of carcinoma of the fundus solely by irradiation. Thus, it cannot be said that we have picked our cases. We have now 72 cases on record.

The great difficulty, as Dr. Martin has pointed out, has been the adequate distribution of radium, and getting the radium in contact with the tumor-bearing area of the uterus. This certainly cannot be done if one uses a straight, tandem uterine applicator.

Several years ago I was impressed by Heyman's work in the use of multiple lead capsules of radium packed into the uterus. I have been employing that method.

Dr. Martin's ingenuity is well known to all of us, and, certainly, the type of applicator which he has shown us this morning is of decided advantage. We may pack the capsules of radium in very successfully, but holding them there is quite a different problem. However, as Dr. Martin has shown us, his holder actually holds the capsules in place.

When one begins to study the statistics of carcinoma of the corpus of the uterus, he must consider first the tissue grade. If I should treat 100 cases of adenoma malignum, Grade 1, of corpus carcinoma, I should approximate 100 per cent cures, because one can get that with well done curettage, hysterectomy or irradiation. If I step over into adenoma malignum, Grade 2, I should expect, again, a high percentage of cures, just as the surgeon would expect through simple hysterectomy. When we go over to adenocarcinoma of Grade 3, quite a different problem presents itself. Dr. Arneson has made quite an intensive study on this particular point, that is, the amount of residual carcinoma found in the uterus following supposedly adequate irradiation. I think that about 50 per cent of the cases still revealed carcinoma cells. Of course, the question comes up as to whether or not these were viable carcinoma cells.

When we treat anaplastic carcinoma, a different problem again presents itself. It certainly is an irradiation problem. So, if one wishes to make use of surgery in addition to irradiation, I should think that adenocarcinoma would be the only type of case in which this would hold true.

I should like to call your attention to an article by Dr. Healy, in which he reported 113 cases before the American Gynecological Society at Pittsburgh. It appeared in the *American Journal of Obstetrics and Gynecology* a few years ago. He showed 100 per cent cure by three methods, and also 100 per cent cure in Grade 2, and so on down the line. In his final summation, he said that it would appear that the use of surgery places an additional handicap upon the patient because patients who had adenocarcinoma of the fundus, that is, frank adenocarcinoma, showed a smaller survival rate than the other types.

Not very long ago, this year, I heard Mason, from Rochester, say that if all the cases of carcinoma of the fundus of the uterus were treated solely by irradiation, without an attempt to pick cases, in the end the highest results would be secured from irradiation. That is a very valuable point to be remembered.

Dr. Axel N. Arneson, St. Louis, Mo.—Evidence of the effectiveness of irradiation in the treatment of corpus cancer is shown in the numerous publications of recent months. It should be noted, however, that radium treatment of endometrial lesions is not a simple procedure. Dr. Martin has demonstrated that an intrauterine tandem is rarely adequate. He has devised a very ingenious method employing multiple tubes of radium that will deliver a more uniform distribution of radiation. By that means, greater amounts can be administered to the tumor, which, in turn, will result in a greater number of cures. We have had experiences comparable in many respects with the earlier ones noted by Dr. Martin. In the attempt to distribute multiple capsules throughout the uterine cavity, it was soon found that they would frequently slip down into the lower segment, or form an irregular group in the center of the uterus. This difficulty has been partially overcome by using two strips of quarter-inch gauze. One is folded over the first capsule introduced into one horn. The other is folded over the second capsule inserted into the opposite horn. By alternating radium capsules with some of the gauze it has been possible to maintain all of the tubes in a more permanent position. Other difficulties have been encountered in the attempt to hold radioactive sources in the cervical canal. This has been overcome by using a short intracervical tandem held in place with the ends of the two gauze strips.

In the radiation treatment of corpus cancer the dose delivered to the adnexal regions is of great importance, because metastases to the tubes and ovaries are not uncommon. The use of multiple capsules presents one of the most logical methods for increasing the dose reaching those regions. Because of the risk of inadequate treatment, we have not yet eliminated hysterectomy among patients suited to surgery. Removal of the uterus is carried out after preoperative x-rays and radium. To evaluate statistics, however, it seems essential that we present our data in a manner that will permit a comparison of radiologic and surgical results upon a uniform type of material. Among the early cases treated with radiation, the attempt should be made to segregate the patients into those suited in every way to surgery, and those not suited to hysterectomy because of some constitutional disorder.

It is essential that we adopt Dr. Martin's method or some other technic for multiple sources containing small amounts of radium in the treatment of corpus cancer. Following the use of that method we may expect improvement in clinical results. It is possible that further advance in radiation treatment may, in time, eliminate the need for hysterectomy in suitable instances.

ANALYSIS OF INTRACUTANEOUS TESTS ON 309 PATIENTS FOR LYMPHOGRANULOMA VENEREUM AND CHANCROID*

By HARRY M. ROBINSON, M.D.
Baltimore, Maryland

I have attempted to study the specificity of the Frei[1] test for lymphogranuloma venereum and the Ito-Reenstierna[2 3] test for chancroid.

ANTIGENS USED FOR THE FREI TEST

My human antigens used for the Frei test were prepared in the usual manner from pus aspirated from fluctuant but unruptured inguinal buboes.

The properly diluted material was stored in rubber capped vials. Before each use, surgical tincture of iodine was applied to the rubber stopper, and care was taken not to inject air into the vial. Utilizing these two simple precautions, it has been possible to keep the antigens sterile and potent in as large as 50 c. c. vials for at least four years, during which time contents were being constantly withdrawn.

Not all samples of pus are utilizable as antigens. In our material, pus was obtained from sixty-one fluctuant but nonruptured buboes with clinical characteristics thought to be lymphogranuloma venereum, each of which occurred in patients with positive Frei tests. Of these specimens of aspirated pus prepared as antigens, fifteen were completely nonantigenic, thirty-one caused only moderately positive reactions when tested in known positive Frei cases, and fifteen were completely acceptable as potent Frei antigens.

The mouse brain antigen* was also used and where used with control mouse brain material, the result could be read satisfactorily as negative or positive without confusion from the nonspecific papule of the control.

ANTIGENS USED FOR CHANCROIDAL TESTS

The nonspecific foreign body reaction caused by the intradermal injection of pus as in the Frei test may usually be avoided in the Ito test. I have employed three antigens in the Ito test, namely "dmelcos vaccine,"† and two samples of American-prepared bacterial vaccine.‡ The reactions produced by these three antigens were identical in my hands.

TECHNIC OF THE TEST INJECTION

Separate tuberculin syringes were used for Frei antigen and chancroidal vaccine. The test substance was injected intradermally on the skin of the forearm in the amount of 0.1 c. c., producing a wheal-like lesion (*Fig. 1*).

READING THE REACTIONS

In my experience, as in that of others, the best time to read the test is 48 to 72 hours after the intradermal injection.

In view of the high percentage of positive results reported in this material, it is of extreme importance to define exactly what I have meant by a positive test. Four types of reaction are, in general, observed:

(1) The site of injection remains free from any area of erythema or induration. This reaction is obviously read as negative.

(2) Nonspecific foreign body reactions may result from the injection either of Frei antigen (sterile diluted pus from human buboes) or from mouse brain antigen and less frequently

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*Read in Section on Dermatology and Syphilology, Southern Medical Association, Thirty-Third Annual Meeting, Memphis, Tennessee, November 21-24, 1939.

*From the Department of Dermatology, University of Maryland.

*Thanks are due to the Lederle Laboratories for the necessary supply of mouse brain antigen.

†Trade name for a product obtained from Poulenc Freres, Inc.

‡One furnished by Dr. A. F. Coca and the Lederle Company, and the second by Sanderson & Greenblatt, to each of whom thanks are due.

from the chancroidal vaccines. These papules, illustrated in *Figs. 2* and *3*, rarely exceed 5 mm. in diameter, with a central area of induration, but without a surrounding areola of erythema. These are also read as negative.

(3) With all of the antigens used in both Frei and Ito tests, there occur nodules 0.5 to 1 cm. in diameter or slightly larger with surrounding erythema varying in size from 1 to 4 cm. in diameter, but without central vesiculation or necrosis. These reactions I have read as positive (*Fig. 4*).

(4) In the severer type of reaction illustrated in *Figs. 5, 6* and *7*, there occurs a nodule with central vesiculation followed by ulceration and necrosis, the area of surrounding erythema often measuring 4 to 6 cm. in diameter. In this type of reaction complete disappearance may require from 2 to 4 weeks. About 15 per cent of the positive reactors in my series presented reactions of this type.

THE MATERIAL STUDIED

The Frei test for lymphogranuloma venereum has been applied in 309 patients, in 211 of whom an Ito-Reenstierna test for chancroid was also performed. The total material divides itself readily into three groups, as shown in *Table 1*: 108 control cases (excluding an additional 11 infants and children, to be mentioned later), in whom no history suggesting lymphogranuloma venereum or chancroid was recorded and who presented no obvious clinical manifestations of these diseases (hereafter referred to as controls); 179 patients with clinical manifestations thought possibly or probably to be due to lymphogranuloma venereum (153) or chancroid (26) (this group hereafter referred to as suspects); and 11 patients clinically diagnosed as granuloma inguinale.

Table 1

COMPARATIVE RESULTS OF FREI AND ITO TESTS IN ENTIRE SERIES

Clinical Diagnosis	Frei Test		Ito Test	
	Cases Tested	Per Cent Positive	Cases Tested	Per Cent Positive
Controls (adults) without history or physical evidence of either lymphogranuloma venereum or chancroid	108	30.5	84	28.5
Patients with clinical manifestations possibly or probably due to lymphogranuloma venereum	153	66.6	86	52.3
Chancroid	26	76.9	19	73.7
Granuloma inguinale	11	72.7	11	54.5
Children (miscellaneous diseases)	11	0	11	0

The study as a whole is, of course, concerned with the specificity and sensitivity of the Frei and Ito tests and their practical value in diagnosis. On inspection of *Table 1*, one is at once impressed with the high proportion of positive tests in the control group and in granuloma inguinale, and conversely the relatively low proportion of positive Frei and Ito tests in patients suspected of lymphogranuloma venereum or chancroid. Although the findings in the latter group may indicate lack of diagnostic acumen in the examiner, nevertheless these data deserve further analysis.

The Control Group.—The patients were tested from random samples of a hospital population drawn from three sources:

(1) Patients with various stages of syphilitic infection; (2) patients thought to be non-syphi-

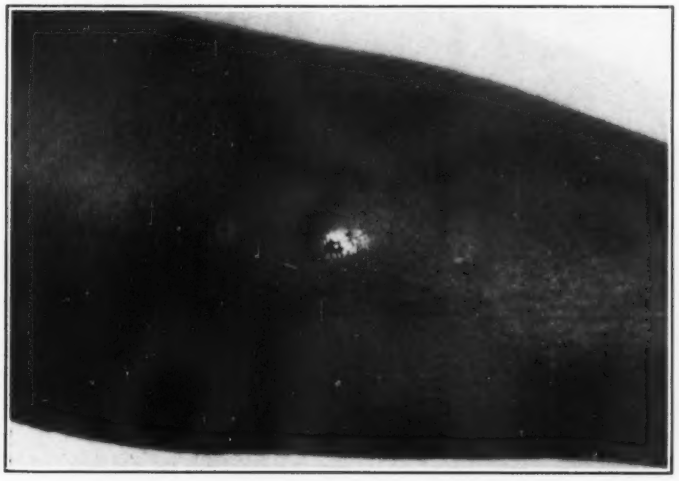

Fig. 1
The wheal-like lesions produced by the intradermal injection of the Frei antigen and chancroidal vaccine.

litic but with miscellaneous medical, dermatologic, gynecologic, or obstetrical cond.tions; (3) negro infants or young children. The histories and physical data regarding the possible past or present existence of either lymphogranuloma venereum or chancroid in the patients of this control group are often inadequate, since histories were taken and physical examinations performed by many different observers. It may be said, however, that the patients did not complain of genital sores or buboes.

The eleven children were uniformly negative to both tests. This is perhaps to be expected since all the patients in this group were under the age of sexual activity. Seven of the eleven mothers of these children were also tested with both tests. Six of these were negative to both; one was positive to the Ito test only. Negro children were especially selected in order to determine, if possible, whether race *per se* was a factor in the production of positive tests (in view of the high proportion of positive results obtained in negro adults later to be discussed).

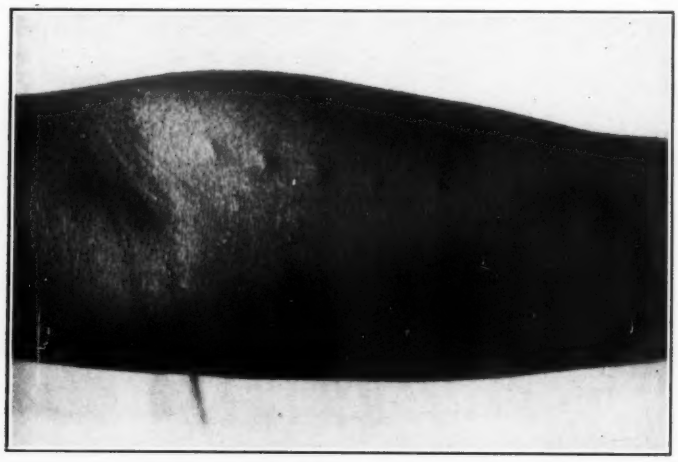

Fig. 2
Nonspecific papules to mouse brain material, mouse brain antigen, human antigen and chancroidal vaccine.

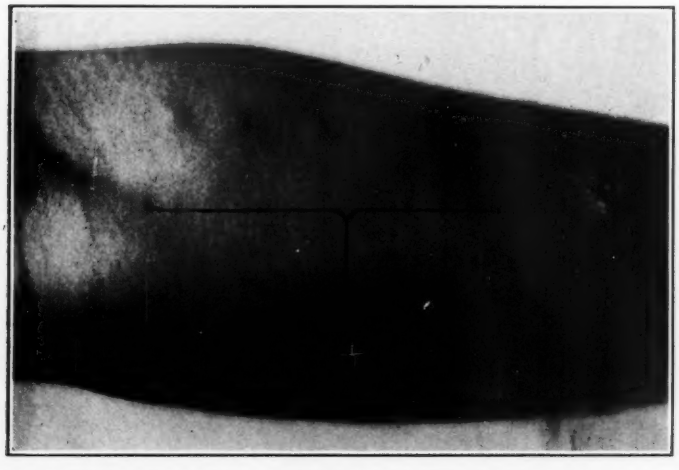

Fig. 3
A. Nonspecific papules to mouse brain material, mouse brain antigen and human antigen.
B. Strongly positive reaction to Ducrey vaccine.

Among the control adults tested there is a striking difference between the syphilitic and non-syphilitic groups. In the former, positive Frei and Ito tests are approximately three times as frequent as in the latter. This phenomenon is subject to three possible interpretations:

(a) The presence of syphilis may cause false positive Frei and Ito tests.

(b) The positive Frei and Ito tests may represent actual infection with lymphogranuloma venereum and/or chancroid, which must, for the most part at least, be entirely symptomless. Although, as pointed out above, history and physical examinations were in most cases inadequate to rule out past or present evidences of these diseases, at least the patients offered no spontaneous complaints suggesting them. It follows further that if the presence of these diseases be assumed, infection with one or both of

them frequently produces a false positive serologic test for syphilis. This hypothesis is untenable since many of the patients in this category conclusively presented (or had previously presented) physical as well as serologic evidence of syphilitic infection.

(c) The Frei and Ito tests may be specific, as in (b) above, and presumably symptomless infection with lymphogranuloma venereum and chancroid is often associated with infection with syphilis.

The first possibility suggested above, that syphilis may cause false positive Frei and Ito tests, will be further examined in the group of lymphogranuloma venereum and chancroid suspects. If either the second or third hypothesis is true, the incidence of symptomless infection with both lymphogranuloma venereum and chancroid may be extraordinarily high, indeed much higher in the general negro population than the incidence of syphilis itself. It must be admitted that in the very large number of supposedly control cases with positive Frei and/or Ito tests, the negative history of lymphogranuloma venereum or chancroid has not been checked by a single observer, the negative statements of patients being gathered from histories taken in many hospital departments. Nor have the positive reactors been searchingly examined for active or inactive evidences of these two diseases by a single trained person. Nevertheless, the patients in this group, if infected, were not at the time of testing and presumably never had been seriously inconvenienced by these diseases.

In the group of lymphogranuloma venereum and chancroid suspects, both Frei and Ito tests were also positive in approximately 20 per cent more syphilitic than in non-syphilitic patients. Were this phenomenon true only of the control group, one might postulate that patients with syphilis are more likely to have other venereal diseases than non-syphilitics, and that therefore the positive Frei and Ito tests are of real significance. Where the same statistical difference appears in the lymphogranuloma venereum and chancroid suspect group, however, it may indicate that syphilitic infection *per se*, in the absence of lymphogranuloma venereum or chancroid, may possibly increase skin sensitivity to the antigens of these diseases.

Table 2

THE RESULTS OF FREI AND ITO TESTS IN 130 CONTROL PATIENTS WITHOUT PHYSICAL EVIDENCE OF LYMPHOGRANULOMA VENEREUM OR CHANCROID

Type of Patients	Cases Tested	Frei Test Per Cent Positive	Cases Tested	Ito Test Per Cent Positive
Syphilitic adults	85	43.5	60	43.3
Non-syphilitic adults with miscellaneous diseases	34	11.7	35	11.4
Infants and children with miscellaneous diseases	11	0	11	0
Total	130	31.5	106	28.3

Table 3

THE POSSIBLE EFFECT OF SYPHILIS IN PRODUCING POSITIVE FREI AND ITO TESTS

Group		Frei Test		Ito Test	
		Cases Tested	Per Cent Positive	Cases Tested	Per Cent Positive
Clinical manifestations possibly or probably due to lymphogranuloma venereum	Syphilitic	69	75.3	37	64.9
	Nonsyphilitic	84	58.8	49	42.8
Chancroid	Syphilitic	17	88.2	13	92.3
	Nonsyphilitic	9	55.5	6	33.4
Granuloma inguinale	Syphilitic	8	75.0	7	57.2
	Nonsyphilitic	3	66.7	4	50.0
No clinical evidence of chancroid or lymphogranuloma venereum	Syphilitic	77	40.2	53	42.4
	Nonsyphilitic	31	6.4	31	6.4
Infants and children (with miscellaneous diseases)	Syphilitic	0	0	0	0
	Nonsyphilitic	11	0	11	0

THE INFLUENCE OF RACE AND SEX ON POSITIVE FREI AND POSITIVE ITO TESTS

In *Table 4* is shown the relationship of race and sex to the incidence of positive Frei and Ito tests in the two groups, lymphogranuloma venereum and chancroid suspects and controls. In both races and both sexes, approximately 30 per cent more patients show positive Frei and Ito tests when clinical manifestations suggesting lymphogranuloma venereum or chancroid are present than in controls. Among lymphogranuloma venereum and chancroid suspects, negroes show positive tests about twice as frequently as do white patients with identical clinical conditions. Among controls, the incidence of positive tests is more than three times as common among negro males as among white males, and almost ten times as frequent among negro females as among white females.

Fig. 4
A. Nonspecific papule to mouse brain material.
B. Positive papular reaction to mouse brain antigen.
C. Positive papular reactions to human Frei antigen.
D. Nonspecific papules to Ducrey vaccine.

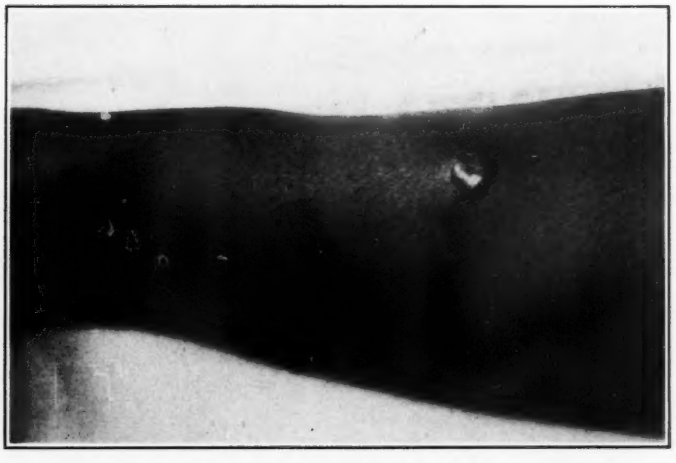

Fig. 5
Strongly positive reaction to dmelcos vaccine with the formation of a large bleb with an area of induration and erythema.

Since the incidence of venereal disease in general, especially syphilis, in negroes as contrasted with white patients follows these same general proportions, one might conclude that so likewise are lymphogranuloma venereum and chancroid equally more frequent in the colored race. Nevertheless, the higher proportion of positive tests among negro lymphogranuloma venereum and chancroid suspects than among similar patients of the white race suggests that race *per se* may be a possible cause of false positive Frei and Ito tests.

The Results of Frei and Ito Tests Among Lymphogranuloma Venereum and Chancroid Suspects.—These data are presented in *Table 5*. The possible or probable clinical manifestations of lymphogranuloma venereum and chancroid divide themselves readily into six groups.

(1) *Frei and Ito tests in Lymphogranulomatous or Chancroidal Genital Lesions or Bubo.*—Eighty-seven patients with genital lesions or bubo conforming to the usually accepted clinical descriptions of lymphogranuloma vene-

reum or chancroid were tested with the Frei test; and in 48 of these same patients the Ito test was also done. The incidence of positive Frei tests was 75.9 per cent; of positive Ito tests, 47.9 per cent. The clinical differentiation between chancroidal and lymphogranulomatous genital lesions or buboes was in this material unsatisfactory; clinical diagnoses were made by many different observers, some of whom at least were inexperienced in the field. The patients were not examined by a single observer, no bacteriologic studies were made, and follow-up examinations to rule out syphilis were often inadequate. It is obviously impossible to conclude from these data whether the two skin tests are of any value in differentiating lymphogranuloma venereum and chancroid buboes from each other, because when positive they do not necessarily indicate either diagnosis, since both tests are frequently positive in the absence of all gross clinical manifestations (*Table 1*), and frequently both tests are positive in the same patient.

(2) ***The Frei and Ito Tests in Patients with Rectal Stricture.***—This lesion, found most frequently in negro women, is generally agreed to be a late sequel of lymphogranuloma venereum, and rarely to be due to any other cause. Among 32 patients with rectal stricture, 78.4 per cent had positive Frei tests, while of 16 of these subjected to the Ito test 50.0 per cent reacted positively.

The same comments made above as to the value of the two tests also apply here.

(3) ***The Frei and Ito Tests in Patients with Other Rectal Diseases, Possibly Lymphogranuloma Venereum.***—Included in this group are 7 patients with ulcerative proctitis or colitis. All were tested with Frei antigens; 42.0 per cent reacted positively. Five of the group also had Ito tests; 80.0 per cent of these were positive.

Here the incidence of positive Frei tests was little greater than in the control group (*Table 1*); while the incidence of positive Ito tests was so high as to offer the astounding and clinically unacceptable conclusion that ulcerative proctitis and/or colitis may often be due to chancroid.

Table 4

THE INCIDENCE OF POSITIVE FREI AND ITO TESTS AS AFFECTED BY RACE AND SEX

Race and Sex	Controls				Lymphogranuloma Venereum Suspects				Chancroid				Granuloma Inguinale			
	Per Cent Positive				Per Cent Positive				Per Cent Positive				Per Cent Positive			
	to Frei		to Ito		to Frei		to Ito		to Frei		to Ito		to Frei		to Ito	
White male	(15)	13.3	(13)	15.4	(9)	22.2	(5)	40.0	(4)	50.0	(2)	50.0	(2)	100.0	(1)	100.0
White female	(16)	6.3	(13)	15.4	(8)	37.5	(3)	33.3	(2)	100.0	(3)	33.3	(0)	0	(0)	0
Negro male	(31)	25.1	(23)	39.1	(46)	71.7	(23)	56.5	(12)	83.3	(8)	87.5	(4)	75.0	(4)	50.0
Negro female	(57)	28.1	(46)	23.9	(90)	71.1	(55)	52.7	(8)	75.0	(6)	83.3	(5)	60.0	(6)	50.0

Table 5

THE RESULTS OF FREI AND ITO TESTS IN 179 PATIENTS WITH CLINICAL MANIFESTATIONS POSSIBLY OR PROBABLY DUE TO LYMPHOGRANULOMA VENEREUM

Manifestation	Frei Test		Ito Test	
	Cases Tested	Per Cent Positive	Cases Tested	Per Cent Positive
Genital lesions or bubo	87	75.9	48	47.9
Rectal stricture	32	78.4	16	50.0
Other rectal diseases, possibly lymphogranuloma venereum (proctitis, colitis)	7	42.0	5	80.0
Other rectal diseases probably not lymphogranuloma venereum	13	76.9	10	30.0
Pelvic inflammatory disease	34	44.1	23	82.6
Obscure genital lesions	6	50.0	3	66.7
Total	179	68.2	105	56.1

(4) *The Frei and Ito Tests in Patients with Other Rectal Diseases Probably Not Due to Lymphogranuloma Venereum or Chancroid.*—The 13 patients in this group comprise a miscellaneous congeries of rectal diseases, ranging from hemorrhoids to carcinoma of the sigmoid. In spite of this, Frei tests were positive in 76.9 per cent, nearly as high a proportion as in patients with rectal stricture; and Ito tests were positive in 30 per cent of the patients in whom they were performed

Apparently the use of these two skin tests by those not competent to evaluate all factors concerned may lead to erroneous diagnoses in patients with non-lymphogranulomatous or chancroidal rectal diseases.

Fig. 6

Strongly positive reactions to Ducrey and dmelcos vaccines with the formation of blebs and induration with erythema. Test with Frei antigen, negative.

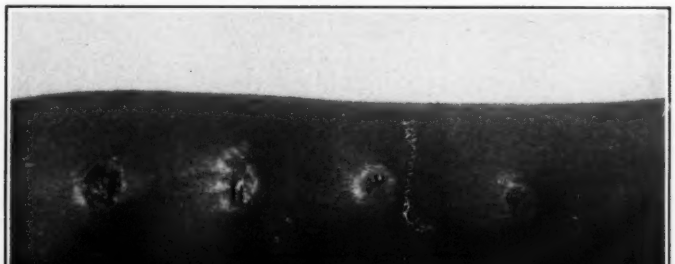

Fig. 7

A. Strongly positive reaction to mouse brain Frei antigen, in which the vesicle was followed by ulceration.

B. Strongly positive reactions to three human Frei antigens with the formation of blebs and ulceration.

C. Positive reaction to the chancroidal test with the formation of a red nodule 1 cm. in diameter.

(5) *The Frei and Ito Tests in Pelvic Inflammatory Disease.*—The etiology of pelvic inflammatory disease may be determined in many instances only with the greatest difficulty, after operation and with careful pathologic and bacteriologic studies. Even these may fail absolutely to establish the cause. It has long been assumed by gynecologists on the basis of direct or collateral evidence, that the majority of cases were gonorrheal or tuberculous in origin. Recently the literature has contained suggestions[4] that some or many such cases of this condition may be lymphogranulomatous. Accordingly, 34 such patients were tested with Frei antigens, 44.1 per cent of whom were positive; and 23 of these were also tested with chancroidal antigens, 82.6 per cent of whom were positive.

These data lend but little support to the idea of the lymphogranulomatous origin of pelvic inflammatory disease, since only about 10 per cent more patients have positive Frei tests than a control group of negro women have. On the contrary, the figures do offer the clinically unacceptable suggestion that pelvic inflammatory dis-

ease may be chancroidal in origin or that such patients may have both diseases concurrently.

(6) *The Frei and Ito Tests in Patients with Obscure Genital Lesions.*—Six patients fall in this group (*Table 5*); but the results add nothing to the information already presented as to the specificity of Frei and Ito tests.

The Frei and Ito Tests in Chancroid and Granuloma Inguinale.—The Ito test is said to be specific in chancroid. In our material there were 26 patients in whom this clinical diagnosis was made. It was bacteriologically verified in none; but the lesions were thought by an observer to be probably or possibly due to chancroid, and were often complicated by supposedly chancroidal suppurating buboes. Unfortunately, in my hands, the Ito test was positive in only 73.7 per cent of 19 cases, while the Frei test was positive in the higher proportion of 76.9 per cent of 26 cases tested (*Table 6*).

Table 6

THE FREI AND ITO TESTS IN 26 CASES CLINICALLY DIAGNOSED AS CHANCROID

Cases Tested	Frei Test Per Cent Positive	Cases Tested	Ito Test Per Cent Positive
26	76.9	19	73.7

The two tests were also valueless in the differentiation of granuloma inguinale from other venereal diseases. Eleven cases in my series were clinically diagnosed as this condition though in only a few was the impression verified by the demonstration of Donovan bodies. In this group, the Frei test was positive in 72.7 per cent, the Ito test in 54.5 per cent of those tested (*Table 7*).

Table 7

THE FREI AND ITO TESTS IN 11 CASES CLINICALLY DIAGNOSED AS GRANULOMA INGUINALE

Cases Tested	Frei Test Per Cent Positive	Cases Tested	Ito Test Per Cent Positive
11	72.7	11	54.5

DISCUSSION

The Specificity of the Frei and Ito Tests.—From the theoretical standpoint, these results may be interpreted in two ways:

(1) The tests are specific for the diseases lymphogranuloma venereum and chancroid. If this is true, the incidence of these two diseases in the population must be much more widespread than that of syphilis. They are from 3 to 10 times as common in negroes as in white patients; and about 20 per cent more frequent in patients with syphilis than in those without. Moreover, patients who acquire any venereal disease, whether syphilis, gonorrhea (pelvic inflammatory disease), granuloma inguinale, lymphogranuloma venereum or chancroid, are excessively prone to acquire lymphogranuloma venereum and/or chancroid likewise, and presumably often simultaneously. Still further, patients with various forms of rectal disease not commonly thought to be associated with either of these two venereal diseases, for example, hemorrhoids, ischiorectal abscess, carcinoma, must have these diseases in a much higher proportion than patients with other nonrectal diseases.

Finally, if these tests are specific, the two diseases, lymphogranuloma venereum and chancroid, may often be acquired in a wholly symptomless manner, and skin sensitivity thereto may persist for years and even for a lifetime without the development of any obvious disease process.

(2) The tests may be nonspecific, positivity being influenced by a number of possible factors, among which may be the age of the patient (children negative), race (negroes more frequently positive than white patients), and the coexistence of other venereal diseases.

CONCLUSIONS

(1) The Frei and Ito tests, as performed in my material, seem to be of little practical value in the diagnosis of lymphogranuloma venereum and chancroid, but may indicate that the diseases are present.

(2) A positive Frei test and/or a positive Ito test may mean that the patient has at the time of the testing, or has had at some past period, lymphogranuloma venereum and/or chancroid.

(3) A positive Frei test and/or a positive Ito test does not necessarily mean the presence of active lymphogranuloma venereum and/or chancroid.

(4) The diagnosis of lymphogranuloma venereum depends upon the proof of the presence of the causative virus by making an antigen of the pus and testing it on a known case of lymphogranuloma venereum.

(5) A negative Frei and a negative Ito test are probably presumptive evidence that the pa-

tient has not at the time of testing, or never has had, either lymphogranuloma venereum or chancroid.

(6) The high incidence of positive Frei and Ito tests in patients without clinical manifestations indicates that more work should be done on control patients.

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DISCUSSION (*Abstract*)

Dr. Robert B. Greenblatt, Augusta, Ga.—Enticing a gynecologist to appear before this Section is like asking the sheep to lie down with the lion. I was forewarned that there would be a bombshell here; indeed, there was a bombshell, but it failed to explode. It was only a dud.

We appreciate the work done by Dr. Robinson. It is important and necessary, and we agree with the statistical data. His figures may be a little higher than ours, but we, too, have found an incidence, say, of 25 per cent of our patients, with a positive Ito as well as Frei test. I have no fault to find with Dr. Robinson's statistical data. The fault I have to find is in the interpretation of these tests and the implications, because if we are to judge and evaluate these tests as Dr. Robinson would have it, the tests are of no value whatsoever. Surely those of us who believe in the Frei and in the chancroid skin test feel that this is not the case.

As regards the Frei test, I do not believe there are many who fail to believe that the test is specific. I know there have been some controversies recently concerning the mouse brain antigen. I am certain that, as the mouse brain antigen is better standardized and foreign material is removed, the test will be as specific as the bubo pus antigen that is prepared in private laboratories.

We have recently studied 50 negroes who presented no active lesions or past evidence of lymphogranuloma venereum, but who did give a positive Frei test. We tried to determine whether our Frei test was giving us a false reaction. Dr. Robert Brandt, United States Public Health venereal disease research fellow at the University of Georgia, prepared an antigen not from bubo pus, but from nonspecific pus in exactly the same fashion as one would prepare Frei antigen. He tested these same 50 individuals and in only two or three of these cases was he able to obtain a nonspecific reaction with the nonspecific pus. We must, therefore, feel that the positive Frei reaction in these cases represents some past infection. One glaring loophole is brought to light in Dr. Robinson's paper. He unwittingly made the tacit admission that the Frei test is specific. How else can he reconcile the following two statements: (1) children of non-venereal age react negatively to the Frei test; (2) in the preparation of Frei antigen from bubo pus, the antigen must react positively in a known case of lymphogranuloma venereum.

Concerning the chancroid skin test or the Ito test, I am leaving some of the remarks on the bacteriologic studies to Dr. Sanderson, but I must stress that we have backed up our cases by bacteriologic studies. Every bubo is aspirated and an attempt to cultivate micro-organisms is made. Dr. Robinson admitted that that is not a procedure at his clinic, or at the clinic from which his material was obtained. I can say that in every case where we isolated the Ducrey bacillus a strongly positive chancroid reaction was obtained when skin testing was done.

There is a source of error which I should like to explain at this time and which may account for the great incidence of double reactions in many of these patients. Many patients with an acute infection, whether it be chancroid or lymphogranuloma venereum, will react positively to both tests. With one of the tests the reaction is usually stronger. The other test may be weak or strong. We have tested these very same patients a week or two later when the acuteness of the disease subsided. One of the tests became negative and the test that remained positive evidently indicated the disease. Occasionally both tests remained positive, meaning that either both diseases were present or that only one was present now and the other occurred in the past. Brandt and Torpin's paper, soon to be published, satisfactorily explains such occurrences.

How can we explain this temporary reaction in these cases? We know that in testing patients for hay fever, although they may be sensitive, let us say, to red top, they may have a positive skin reaction to some grass that is related to it. We know that although patients with asthma may be sensitive to one food a positive skin reaction may be obtained with another food in spite of the fact that they are not really sensitive to it. I think this reaction was described some time ago, and it is known as Moro's parallergic response. We explain the temporary reactions in our cases on the same basis. I know, for example, that in testing some 100 patients for chancroid disease with the Ito test, patients whom we felt had no evidence and never had any evidence of chancroid disease, all of them white women, we never had a false reaction except in those cases that had a history of asthma or some other allergy. In one case there was bronchial asthma. In two cases there was evidence of moniliasis and they gave a positive reaction to the oidiomycin skin test.

I feel, as one who with Dr. Sanderson is responsible for the commercial Ducrey vaccine that is on the American market, that there is a need for this vaccine and that the practitioner should be given the opportunity to use it. I can confidently and emphatically assert that the test is as accurate in our hands as any of the skin tests that are in general use. Interpretation is important. We are not robots. Every test must be evaluated and our clinical senses must be brought into play.

However, we, too, have come more or less to the same conclusion as Dr. Robinson, and the following is the summary from our paper published in 1937 in the *Archives of Dermatology and Syphilology:*

"A warning note is sounded to investigators who report cases of lymphogranuloma venereum on the basis of a positive Frei test without performing a concurrent chancroidal test. Twenty-four patients in a group of 80 patients exhibiting a positive reaction to the chancroidal test also had a positive reaction to the Frei test; this emphasized the need for caution in the interpretation of the results of these tests.

"A positive chancroidal test is only presumptive evidence and does not necessarily mean that the lesion under consideration is chancroidal. A similar conclusion should be borne in mind in the interpretation of a positive Wassermann as well as of a positive Frei test in every case of genital lesion unless other confirmatory laboratory evidences are present.

"Finally, a negative intradermal test with bacillary antigen is diagnostic so far as it rules out infection by the bacillus of Ducrey. A positive intradermal chancroidal test commits one to the diagnosis of chancroidal infection only when the Frei test, the Wassermann test and microscopic examinations for malignant disease and granuloma inguinale give negative results."

Dr. Robinson did tell me, however, that he is undertaking a further study of these cases. He is going to select 400 new cases and try this work all over again. I am very glad to hear it. His is an inquiring mind; his attitude a courageous one.

Dr. E. S. Sanderson, Augusta, Ga.—I cannot explain completely why there has been this presumable nonspecificity that Dr. Robinson has obtained. His results are there, but as Dr. Greenblatt has pointed out, the question of interpretation is an important factor. From our observations it is true that a number of patients coming to us may have more than one of these infections at the same time. It is also true that many patients have had some of these diseases in the past. I think the consensus among those who have been doing skin tests associated with these infections indicates that they represent antigen-antibody reactions, and such reactions are quite specific.

The great variance between the clinical findings and the Frei tests reported are the first to come to our attention. From the published work in the literature during the past few years, and from numerous personal interviews and communications, this is the first time (exceptions noted by Dr. Greenblatt) that a Ducrey antigen made from a culture of the organisms has been reported to yield false positive skin tests. In the light of these discrepancies, there are possible sources of error which should be given consideration. In the first place, the selection of pus for making Frei antigen. Antigen made from bubo pus obtained from a patient in whom there is a positive Frei reaction does by no means indicate that this pus contains the virus of lymphogranuloma venereum. The condition may be chancroid, and chancroidal pus also contains a specific, if not over-abundant, antigen as evidenced by reference to foreign publications and those of Cole and Levin. The latter used it in lieu of a bacillary suspension because of the inability to culture Ducrey's bacillus, and the non-availability at the time of any bacillary antigen. We, too, have confirmed these findings.

At the outset of our work on lymphogranuloma venereum we were concerned with the preparation of Frei antigen. A criterion for a satisfactory one was that the material should be obtained from a patient yielding a positive Frei test. Numbers of such antigens were made from time to time. Analysis of the accumulated data indicated that in some cases we were obtaining with some antigens negative reactions in patients suspected of having lymphogranuloma venereum, and positive reactions in what were thought to be chancroid. The explanation of these discrepancies was immediately brought to light following the published reports by Cole and Levin concerning the antigenic qualities of chancroidal bubo pus. The dangers of this pitfall forcibly brought to our attention the urgent need for a more careful selection of bubo pus, which in turn was dependent upon more reliable methods for the differentiation of chancroid. The net result of this was a satisfactory method for culturing Ducrey's bacillus, and a method of preparing a skin testing bacillary antigen.

It is often stated that sensitivity to Frei and chancroidal antigens remains positive for years after clinical recovery; and there are those who claim a lifelong sensitivity. Sufficient time has not elapsed for us to substantiate these findings, although a few of our earlier patients who have been retested are still reactive to their specific antigens. As it is customary to standardize one Frei antigen against another, it is clear that one has to be absolutely sure about all antigens: selection of all pus must be only from patients giving positive Frei and negative chancroidal reactions.

Based on several years' data correlating simultaneous intradermal Frei and chancroid tests, cultures of bubo pus, and the microscopic examinations of stained smears for Donovan bodies from ulcers, buboes and granulations, we are firmly convinced that the interpretation of the skin tests as an aid in the differential diagnosis of venereal lesions is highly satisfactory and fully as reliable and as free from error as is any similar skin allergic reaction. It is to be regretted that in the present series no correlated laboratory studies were done.

Dr. Hervey A. Foerster, Oklahoma City, Okla.—The thing that we particularly get from this paper is the name of this important disease. It was first called "tropical bubo," then was given the name "lymphogranuloma inguinale," and then "lymphopathia venereum," which was suggested by Sulzberger. I think that "lymphogranuloma venereum" should be the accepted term used by everyone, because "lymphogranuloma inguinale" is a misnomer. I have seen a case of this in a sexual pervert where the cervical glands were involved and you could hardly describe it as an inguinal disease.

It is rather important here, although it was not in the scope of Dr. Robinson's paper, to have some discussion on the treatment, and I should like to ask Dr. Robinson what forms of treatment he has used and the best results that he has obtained. The mouse brain antigen is about the only substance that is available for the general practitioner to obtain, if he has only a small number of cases and has not access to a large venereal clinic, where he can cultivate the virus.

Dr. Robinson (closing).—Answering the last discussor first, the treatment of lymphogranuloma venereum is so varied that it is nonspecific. I have used many methods of treatment, including the intravenous injection

of mouse brain antigen and human antigen, the oral administration of sulfapyridine and sulfanilamide, fever therapy, and the antimony compounds. Of the antimony compounds, it is my impression that a new compound called anthiomaline may be the most effective of the several I have used. Of the other forms of treatment, I think the best results have been obtained by the intravenous injection of mouse brain antigen, and orally, sulfanilamide and sulfapyridine. I am not quite convinced that these treatments are specific, because there have been many cases which have not responded to any of them.

Concerning buboes, we feel that the best course is to aspirate or excise them. I have obtained much better results by aspirating than by incising or excising them. Naturally one wishes to do all that one can; therefore, in addition to aspirating I also prescribe sulfanilamide or sulfapyridine or the intravenous injection of Frei antigen.

Answering Dr. Greenblatt and Dr. Sanderson, I feel that we have not much of a quarrel because, if our data are more or less alike, it is only a question as to what conclusions we draw from them. I realize that Drs. Greenblatt and Sanderson are to some extent definitely interested in the commercial preparation and distribution of the Ducrey vaccine. I wish to stress that in my hands it has been a test material as reliable as the dmelcos vaccine.

It was not my intention to indicate that the simultaneous positive reactions to the two tests were due to a nonspecific allergy; about 12 per cent of this group were positive to both tests and remained positive. Some of my patients were tested twice and some three times, and some of those who were negative at first, or doubtful at first, later became positive, but none that was positive ever became negative.

As Dr. Sanderson said, one cannot foretell by the presence of a positive Frei reaction whether the bubo pus of the patient under investigation will make a Frei antigen. That is one of the reasons that I say that these tests are not diagnostic. One must go further and evaluate the pus in each case and, as I mentioned in the first part of my paper, 46 of the specimens of pus aspirated from buboes, when prepared as antigens caused a more or less strongly positive reaction in known cases of lymphogranuloma venereum. Of course there is such a disease as lymphogranuloma venereum and these antigens did react positively in 46 and were labeled "positive antigens." Similarly the Ito test in known cases of chancroid was regularly positive. One must agree with that. I still insist, however, that a positive Frei test and/or a positive Ito test is not diagnostic of the case under investigation. In many of the buboes under investigation the Frei and Ito tests were positive simultaneously, but the pus we made reacted only to one or the other of these conditions, never to both, and in a few instances to neither.

I am convinced that many physicians will fall into the common error of diagnosing suspected conditions on the basis of a positive Frei and Ito test and will become confused should both tests be positive. Let me repeat that a positive Frei and/or a positive Ito test may indicate that either of these diseases is present and that further investigation is needed in each case to diagnose the disease conclusively.

A COMPARISON BETWEEN THE REACTIONS OF THE LARGE PHAGOCYTIC MONONUCLEAR CELLS TO SUBCUTANEOUS INJECTIONS OF INDIVIDUAL LIPIDS AND TO MIXTURES OF THE SAME LIPIDS*

By EDNA H. TOMPKINS, M.D.
Nashville, Tennessee

It has been shown elsewhere[1] that subcutaneous injections of guinea pigs with lipids extracted from brains result in reactions of the tissues which are specific for each chemical group. The reactions are characterized in particular by the response of the phagocytic mononuclear cells, and are so clear-cut that they serve as an indication of the degree of chemical purity obtained in any given extraction.

The extractions of the lipoid substances used for those studies, and for the work to be reported today, were carried out by methods of differential solubility as outlined by McLean and McLean.[2] We are concerned here only with the acetone-insoluble group of lipoids. These are divisible into the ether soluble, and the ether insoluble groups. The ether soluble group contains two classes of phosphatides, the lecithins and the cephalins. The ether insoluble group contains a third class of phosphatides, the sphingomyelins, and likewise the galactolipids, which consist largely of kerasin and phrenosin.

In the course of the extractions it was noted that the impure fractions consisting of mixtures of phosphatides and cerebrosides elicited more striking infiltrations and larger mononuclear cells than did the purified phosphatides. Yet the cerebrosides alone did not call forth mononuclear cells. This discrepancy, and the findings by Bloom,[3] Epstein,[4] Lieb[5] and others of large quantities of kerasin in the organs from cases of Gaucher's disease, were so in contrast to the negative results obtained by injection of the purified cerebrosides that the following studies were undertaken with known mixtures of purified individual lipids.

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*Read in Section on Pathology, Southern Medical Association, Thirty-Third Annual Meeting, Memphis, Tennessee, November 21-24, 1939.

*From the Department of Anatomy, Vanderbilt University School of Medicine.

Three lipid fractions were used for these studies: a preparation of sphingomyelin made from fresh beef brains according to the method of Levene;[6] a preparation of mixed ether-soluble phosphatides, the lecithins and cephalins, freed from ether-insoluble substances; a preparation of the cerebroside, kerasin. The latter two substances were extracted from a crude mixture of brain lipoids donated by Dr. David Klein, of the Wilson Laboratories. The mixture of the lecithins and cephalins was not separated into the components, since it had been shown previously that the reaction of the large mononuclear cells is the same to each one individually. The kerasin was separated by differential crystallizations from a mixture of cerebrosides which, in turn, was freed from phosphatides by twelve crystallizations from ethyl alcohol.

The individual substances and the experimental mixtures of the same substances were injected subcutaneously in guinea pigs or in mice. For purposes of comparison, different materials were usually injected into two areas at the same time. The emulsions for injection were made by dissolving the desired materials in a mixture of alcohol and chloroform, evaporating the solution to dryness and emulsifying the residue in 5 per cent glucose. The resultant emulsion, or suspension, was then sterilized in a steam sterilizer for two hours. When a mixture of the lipids was desired, the individual substances were dissolved together in the alcohol-chloroform solution before emulsification, as more uniform mixtures were obtained by this method than by mixing emulsions which had been prepared individually.

The volume for injection varied from 1 to 2 c. c. The animals were sacrificed at intervals of from three to fourteen days after the injections. Gross estimations were made of the degree of reactions, and of the absorption or residue of the injected materials. Scrapings of the area of injection were stained supravitally with neutral red, and films of the connective tissue about the areas of reaction were also studied supravitally. Blocks were saved for sectioning.

The reactions to the individual lipoid bodies were typical of those previously found to be characteristic of the given fraction. It is necessary to review them briefly in order to contrast the differences in the reactions elicited by the mixtures of individual lipids.

Both of the groups of phosphatides stimulated an active infiltration of large mononuclear cells (*Figs. 1* and *2**) which were characterized by their capacity for growth, by the size and number of their phagocytic vacuoles and by the absence of any signs of degenerative processes. The cells responding to the ether-soluble mixture were slightly smaller than those responding to the sphingomyelin and disappeared more rapidly. The cells which responded to the sphingomyelin had very large vacuoles which were striking for their uniformity of size and color. Often the larger cells in areas injected for several days or more were packed with unstained vacuoles which in all other respects looked like the vacuoles in the stained cells. In addition, the cells frequently contained small rods which appeared in greater numbers as the vacuoles disappeared.

In contrast to the active infiltrations of phagocytic mononuclear cells in areas injected with phosphatides and the rapid disappearance of the latter, the cerebroside was relatively inert and called forth a very indolent reaction merely about the periphery of the mass of injected material (*Fig. 3*). This reaction consisted of an active infiltration of polymorphonuclear cells

**Figs. 1* to *9*, inclusive, are photographs of the subcutaneous tissues of mice following experimental injections of lipids. All, except *Fig. 9*, are from fixed tissues stained with hematoxylin and eosin. 10 x ocular used throughout.

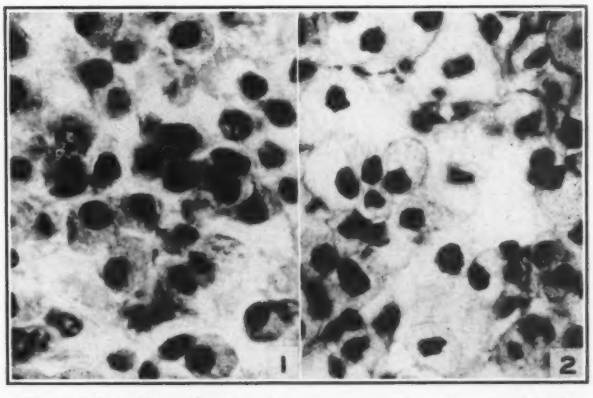

Fig. 1 (left). Macrophages in subcutaneous tissue three days after injection of glycerophosphatides. 1.8 mm. objective.

Fig. 2 (right). Macrophages in subcutaneous tissue four days after injection of sphingomyelin. 1.8 mm. objective.

followed by a mild infiltration of fibrous tissue mingled with small-sized large mononuclear cells (*Fig. 4*). Most of the cerebroside remained apparently unabsorbed and uninvaded for periods of as long as eleven days.

The areas injected with mixtures of cerebroside and either preparation of phosphatide, on the other hand, contained innumerable large mononuclear cells as well as many polymorphonuclear cells. After three to four days the latter disappeared from the reactions, but the large mononuclear cells continued in great numbers for about seven days (*Figs. 5, 6, 7,* and *8*). The character of the reaction with either phosphatide varied somewhat, according to the relative amount of phosphatide to cerebroside. Below a ratio of two parts of the cerebroside to one of sphingomyelin, or one of the cerebroside to two of the more rapidly absorbed ether-soluble mixture, there was usually considerable cerebroside left unabsorbed, and fibrous tissue had an active share in the reaction. Binucleated cells and even giant cells also appeared. Above those ratios, the absorption of the cerebroside was fairly complete, and the large mononuclear cells were very striking in their characteristics. They were always larger than the mononuclears responding to the individual phosphatide at corresponding intervals of time. For the first few days after the injections they were fairly similar to the cells called forth by the individual phosphatide, but with increasing intervals of time, they became very large and eventually reached magnitudes beyond those obtained at any interval of time from the individual phosphatides. Furthermore, other characteristics became manifest as the cells developed which stamped them as under the influence of the cerebroside. The cells in the areas injected with mixtures of sphingomyelin and cerebroside often contained droplets of fat scattered among the vacuoles, and gradually the larger cells came to contain unstained gray bodies of low refractivity such as occurred after sphingomyelin alone. After about seven days, all stained bodies had disappeared and cells were often found containing innumerable small rods, which were stained, beaded or unstained. Due to the chemical similarity between kerasin and sphingomyelin, the assumption cannot be made that the rods were due specifically to the latter substance, although they occurred in far greater numbers than after injections of sphingomyelin alone. From the fact, however, that they also appeared late in the reactions to mixtures of cerebroside with ether-soluble phosphatides it is probable that they represent one of the features incident to the presence of the kerasin.

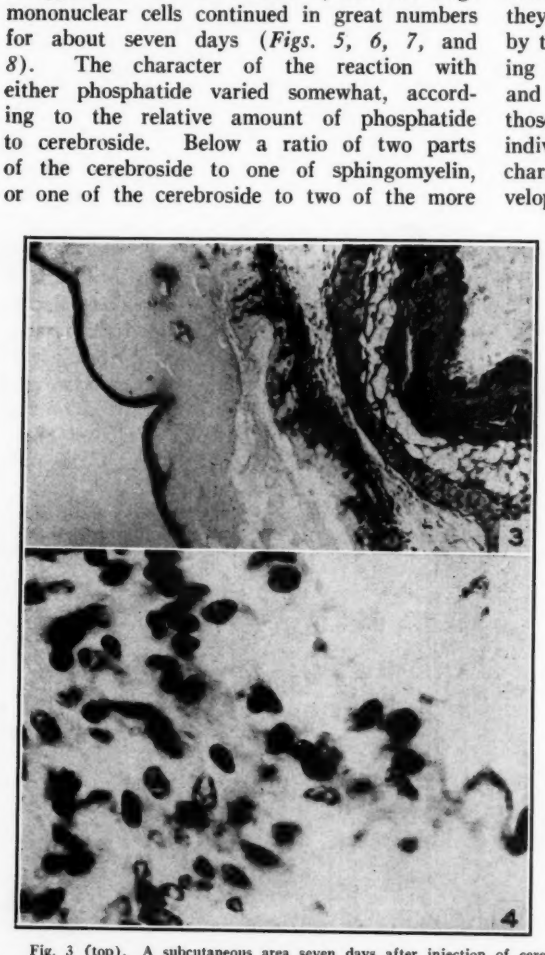

Fig. 3 (top). A subcutaneous area seven days after injection of cerebroside. A fine film of connective tissue surrounds the structureless mass of cerebroside in the center of the field and delicate strands invade it, but otherwise there is very little cellular reaction. 16 mm. objective.

Fig. 4 (bottom). Higher magnification of the area shown in *Fig. 3*. The cells are mostly fibroblasts with a few small macrophages scattered among them. The macrophages are very different from the large vacuolated cells shown either in *Figs. 1* and *2*, or in *Figs. 7* and *8*. 1.8 mm. objective.

The phagocytic mononuclear cells which responded to injections of the cerebroside mixed with the ether-soluble phosphatides were even more striking than after injections of mixtures containing sphingomyelin. Since kerasin is less closely related chemically to the ether-soluble phosphatides than to sphingomyelin, any deviation from the reaction caused by the ether-soluble

phosphatides alone may be regarded as due to the presence of the cerebroside. The mononuclear cells in areas injected with the mixtures of cerebroside and ether-soluble phosphatides developed to greater sizes than were ever achieved after the latter material alone. At about seven days after the injection, innumerable rods began to appear in the cells. They were stained, beaded or unstained supravitally and looked like the rods in the cells following injection of the mixtures with sphingomyelin (*Fig. 9*). In addition, the cells contained unusually large rather oval or spindle-shaped bodies which were of low refractivity, and which were both stained and unstained supravitally. While the color of the stained bodies was not as dark as that of the deposits in the cells following injections with mixtures of sphingomyelin, the size and shape of the deposits, as well as the occurrence of so many unstained ones, presented a morphologic picture which was very similar to that obtained in areas reacting to the mixtures of cerebroside with sphingomyelin.

The fixed tissues from the areas injected with the mixed lipids are gratifyingly corroborative of the conclusions based on the supravital studies (*Figs. 5, 6, 7,* and *8*). They contain extensive infiltrations of very large foam cells quite in contrast to the almost total lack of such infiltrations in the tissues from areas injected with the cerebroside alone (*Figs. 3* and *4*), and yet obviously different from the large mononuclear cells responding to the phosphatides alone. With Mallory's aniline blue stain the cytoplasm of the cells is often wrinkled or fibrillar in appearance and similar to that described for the foam cells found in Gaucher's disease.

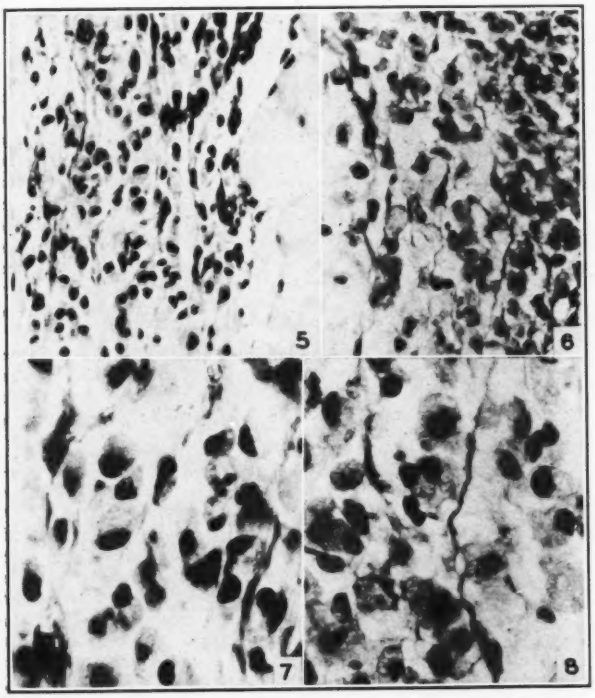

Fig. 5 (top left). Subcutaneous tissue seven days after injection of cerebroside mixed with glycerophosphatides. Compare with the indolence of the reaction to cerebroside alone as shown in *Fig. 3*. 4 mm. objective.

Fig. 6 (top right). From same mouse as photograph shown in *Fig. 3*. Subcutaneous tissue seven days after injection of cerebroside mixed with sphingomyelin. Compare with the indolence of the reaction to cerebroside alone as shown in *Fig. 3*. 4 mm. objective.

Fig. 7 (bottom left). Higher magnification of the area shown in *Fig. 5*. The macrophages have a more striated cytoplasm than do those which responded to glycerophosphatides alone (*Fig. 1*). 1.8 mm. objective.

Fig. 8 (bottom right). Higher magnification of the area shown in *Fig. 6*. The macrophages have a more striated cytoplasm than do those which responded to sphingomyelin alone (*Fig. 2*). 1.8 mm. objective.

In summary, it may be stated that both of the phosphatide fractions, when injected subcutaneously, elicit an almost pure infiltration of large mononuclear cells which are quite distinctive for each chemical fraction, while the purified cerebroside is extremely inert, is very slowly absorbed, and elicits a reaction which is characterized mostly by an infiltration of polymorphonuclear cells followed by an invasion of fibrous tissue and a very few small-sized large mononuclear cells. In contrast, injections of mixtures of the cerebroside with either phosphatide fraction results in rapid absorption of the cerebroside and widespread cellular reactions on the part of the large mononuclear cells, the morphology of which is modified from that of the cells responding to the individual phosphatides alone. The reactions are such as to indicate that absorption of the cerebroside and entrance into the mononuclear cells has taken place in the presence of the phosphatides. The phagocytic cells in areas injected with mixtures of the cerebroside and the ether-soluble phosphatide acquire many of the characteristics of those

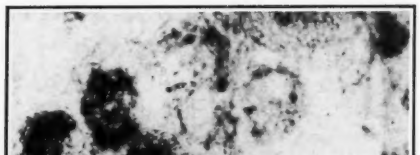

Fig. 9

Supravitally stained film of connective tissue from a subcutaneous area fourteen days after injection of a mixture of cerebroside and glycerophosphatides. Innumerable unstained rods occurred both without and within the cells. There were also rods within the cells which stained homogeneously with neutral red or had a beaded appearance. The stained rods appear black in the photograph. 1.8 mm. objective.

in areas injected with the mixtures of cerebroside and sphingomyelin. The cerebroside is apparently a lipoid body which is unable to stimulate the infiltration of phagocytic mononuclear cells and its own absorption when injected subcutaneously. Mixture with phosphatides, on the other hand, makes possible these activities.

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DISCUSSION (*Abstract*)

Dr. M. Pinson Neal, Columbia, Mo.—It is truly interesting to note the degree and character of the cellular reactions the author has obtained following injections of the derivatives from cerebral tissue and their mixtures.

Pathologists have for years recognized that the large mononuclear cells, the macrophagocytes of Metchnikoff, or, as we prefer to term them, the endothelial leukocytes, have a very highly specialized phagocytic activity for foreign elements, hair, pigments, granules, certain types of bacteria, tissue debris, crystals, degenerating and destroyed erythrocytes and other cells, fat globules and droplets, and the products of disintegrated oils and fats. Their high phagocytic index for tubercle bacilli, the Hansen's bacillus of leprosy, and in typhoid fever for typhoid bacilli, but to a much greater degree for cellular elements, is striking. It would be most valuable to know what does stimulate this remarkable migration and multiplication.

It has been accepted that in damages involving nerve tissue, either of the central nervous system or its processes, the endothelial leukocyte is the agent that phagocytizes and removes by one means or another broken down cell elements, myelin, fatty and nuclear debris, and other material. Theirs is the conspicuous role as reactive cells in all damages, degenerations and necroses that involve cerebral tissue.

It has been our observation that the size of the large mononuclear cell varies widely, depending much upon whether the cell is at rest or at work, and according to the amount and quality of its engulfed material. The pH value and salt content of the fluid in which they are found also cause marked changes in their size, shape, and degree of staining reaction by standard dyes. Such changes or alterations can therefore hardly be considered as specifically indicative of their causation.

The small rods that are discussed as being found within the cell cytoplasm are not identified, nor does the description permit one to draw conclusions concerning them. The question of calcium deposits as intracellular granules arises when one considers that "some of the darker staining granules become most marked when the vacuoles decrease." The essayist describes the mononuclears as being phagocytic, but the particular substances phagocytized have not been fully and definitely defined, or in some instances, named. The cells are said to contain droplets of fat scattered among vacuoles. Since no fat stain apparently was used, I wonder if these might not also be fat in character. Hydropic or serous infiltrations represent changes that cannot be distinguished from deposits of fat globules within cells unless it be done by special preparation and staining.

Dr. Ernest W. Goodpasture, Nashville, Tenn.—Since the work of Mitchnikoff we have considered phagocytosis as being perhaps primarily if not, in the minds of certain advocates, essentially an antagonistic reaction or mechanism to infections of various kinds. There is evidence, however, that under certain circumstances and in association with certain infectious agents this great phagocytic system may offer an environment which is not only favorable but perhaps essential for the development and the course of certain infectious diseases. We are beginning to be more conscious of this system in connection with correlation of bacterial and other parasitic diseases with the virus diseases and with the possibility of an intracellular relationship of infectious agents in general.

It seems to me, for example, in the disease leprosy, that phagocytosis by the leprous cells, instead of being antagonistic, offers a favorable and perhaps an essential environment for the growth of the bacillus of Hansen.

Other analogies can be drawn, for example, the protozoan disease, kala-azar, where the protozoan microorganisms are found essentially in this phagocytic system. There is no evidence that these micro-organisms are growing in the fluids of the body. They are taken up by the cells, and they find in the cells favorable environment for their future growth, and if it were not for this activity growth possibly would not occur.

An example derived from fungus diseases is Darling's histoplasmosis, where the yeast-like form of the parasite which was cultivated by Dr. Demonbreun a few years ago finds a most favorable environment in the reticulo-endothelial system. Whether that is essential or not to this organism we do not know.

It is interesting that in certain of these infectious diseases, where the parasites find apparently a favorable environment within the cell, the etiologic agent is cultivated with great difficulty or has not been cultivated at all. Apparently there is adaptation to the intracellular environment which cannot be duplicated at the present time by artificial conditions.

It is of interest also in certain of the bacterial diseases, fungus diseases and protozoal diseases in which this cellular relationship obtains that immunological response is difficult or impossible. Certainly it is impossible if one judges from the effectiveness of it. It seems to me, while the reticulo-endothelial system can react to certain materials by an antibody response that there are other proteids perhaps which resist the primary phase Dr. Sabin spoke of, and do not respond by an antibody or effective antibody response.

Dr. Florence Rena Sabin, Denver, Col.—I was naturally much interested in these studies of Dr. Tompkins. It is now well known that a phosphatide from the tubercle bacillus transforms the monocyte into an epithelioid cell. I think it was Dr. Tompkins who first brought out the fact that the epithelioid cell does not return to its original form and hence is an abnormal cell. This indicates that the monocyte cannot completely disintegrate tuberculo-phosphatide. I should like, then, to ask if, in the case of the lipids used in these studies, the cell which phagocytized them does, eventually, return to its original form?

There is one other point which I should like to mention in regard to the reticulo-endothelial system in general. In one of Franklin P. Mall's last papers he described the processes of infection in early embryos as different from the reactions of adult tissues in this manner: the early embryos lack neutrophils and hence the reactions involve only the phagocytic mononuclears.

Dr. Tompkins (closing).—I am very glad that Dr. Goodpasture emphasized the importance of the reticulo-endothelial system in general.

In answer to Dr. Sabin's queries, first, polymorphonuclear cells were always present early after all of these injections. The reactions which I discussed today were always at an interval of from three days on. Second, we never did obtain anything comparable to the epithelioid cell. At the period of time when one usually gets an epithelioid cell in the case of the tubercle bacillus and its products, which is usually from six to ten days after the injection, these cells were beginning to fade from the picture. The vacuoles seemed to dissolve and the cells became smaller again, and then faded out. Where they went and, really, where they came from, I am not prepared to say at this time, but they did not break down their droplets and then carry them no further, as the epithelioid cell does. The droplets, and everything, just faded out of the picture. The reaction with sphingomyelin, in particular, showed this effect. At first the vacuoles were all stained and later they became unstained, whatever that may mean. It certainly means that there had been a chemical change going on in that the vacuoles first lost the ability to stain, and then gradually disappeared, and then rods appeared. Whether the rods would finally have disappeared also, I do not know.

Answering Dr. Neal, in regard to the rods: we found them to stain under so few conditions that I do not know what they were. In fixed ti sues, with alcoholic dehydration, they largely disappeared. We analyze the striations which did stain after fixation, as due, perhaps, to spaces left in the cytoplasm rather than to actual bodies still in the cytoplasm. Supravitally, the rods were obviously structures in the cells which sometimes stained deep red with neutral red, but more often were merely unstained bodies, gray, and with a slightly different refractive index from that of the rest of the cell. They looked exactly as the cerebroside itself looks if subjected to supravital dyes on a microscopic slide. The supravital preparations were from scrapings of the tissues, and they contained innumerable crystals of cerebroside in the medium outside of the cells. They were always unstained under those conditions, and always looked like the unstained rods within cells.

In regard to the fat droplets in the cells: I do not mean the specific, big vacuoles that I have been talking about. As the cells reached later ages they frequently contained tiny droplets of a very highly refractive nature which supravitally appeared as neutral fat does, and which stained deeply with sudan 111 and scharlach r. The specific vacuoles I described today incident to the injections which we gave did not stain with sudan 111 or scharlach r. The sphingomyelin vacuoles stained a lilac hue with methylene blue, and at times with Nile blue, but not always with Nile blue. It was usually the older vacuoles, the ones that had lost their ability to stain with the supravital dye, that stained best. Frequently they did not stain at all in the younger cells. Again, we know very little about specific fat stains, really, when we are dealing with individual lipoids mixed with other lipoids. Theoretically, there was no cholesterin in the cells, unless some had been made, and there was no neutral fat. Therefore, theoretically, we were staining the phosphatide directly, and it stained with Nile blue slightly and with methylene blue more deeply, always a lilac color.

I have no evidence in regard to calcium. Dr. Neal brought up many points which I want to study. There are many phases which I have not studied specifically. I do not know what is happening in the cells. It is obvious that the material is undergoing a chemical change, that it is disappearing, that the cells are not disintegrating in the process, and that the material, the cerebrosides, can enter only when the phosphatides are present, and when they have entered something happens, but I do not know the chemical nature of the changes.

EFFECT OF PREGNANT MARE'S SERUM HORMONE ON THE ABNORMAL OVARY*

By LAMAN A. GRAY, M.D.
Louisville, Kentucky

Since the work of P. E. Smith,[1] in 1926, which showed the ovaries to be under the control of the pituitary, our present day understanding of the physiology of the sex glands has developed. The pituitary secretes a hormone which causes the graafian follicle to grow and develop. The follicle in turn secretes the estrogenic hormone which is responsible for growth of the genital tissues in general and the proliferative non-secretory endometrium of the first half of the menstrual cycle in particular. At the time of ovulation, usually from the twelfth to the fourteenth day after the first day of the menses, the pituitary is thought to begin secreting the luteinizing hormone. This causes growth and development of the corpus luteum. The progesterone thus formed produces the progestational or secretory endometrium of the last half of the cycle.

In amenorrhea of long standing, the pituitary may secrete only small amounts of the follicle-stimulating hormone, resulting in ovaries with no activity or small follicles secreting small amounts of estrogenic hormone. Thus the endometrium is atrophic or of only moderately developed non-secretory type. In a separate category belong those cases with temporary amenorrhea and endometrial hyperplasia, theoretically due to a rising or sustained level of the estrogenic hormone. Also, there may be rare cases in which ovulation is proceeding, with an accompanying secretory endometrium.

Metrorrhagia in the large majority of cases (probably 80 per cent) is associated with a non-secretory interval endometrium or with endometrial hyperplasia and its "Swiss cheese" pattern of glands. These two forms may be found in the same patient after short intervals. Hyperplasia is apparently a progression of the estrogenic effect which develops the interval non-secretory endometrium. Lack of ovulation and corpus luteum formation seems the rule in these cases. There are perhaps 20 per cent of bleeding cases which have a secretory endometrium and therefore should have an active corpus luteum. The understanding of this group is more incomplete.

Since this knowledge of uterine pathology has been evolved it has become evident that in amenorrhea and metrorrhagia there are most often lack of ovulation and corpus luteum formation. Substitution therapy with estrogens and progesterone has few adherents. One desires to produce ovulation with subsequent corpus luteum formation to correct these cases.

In 1928, Aschheim and Zondek[2] discovered prolan in human pregnancy urine. This is very potent in stimulating follicles, ovulation and corpora lutea in various laboratory animals, as rats, mice and rabbits, being particularly effective as a luteinizer. Shortly thereafter many investigators reported good results in treating amenorrhea and metrorrhagia, but the experience of succeeding years has brought much disappointment. Jeffcoate,[3] in a recent analysis, sent questionnaires to leading gynecologists. Twenty-one out of twenty-four felt that prolan (anterior pituitary-like hormone of human pregnancy urine) is purely temporary in action and very variable in its remote effects. Jeffcoate personally thought that 66 per cent of cases derived real benefit. This figure would seem high to us. Hamblen[4] shows that this hormone may cause cystic degeneration of follicles and possibly corpus luteum formation in older women. More investigations are indicated using much larger dosages. Prolan, more recently named chorionic gonadotropin because of its origin in the placenta, has not proven satisfactory in regulating the ovaries.

Extracts from hypophyses of animals, particularly sheep, have been of relatively little value because of low potency. In the study of Ross[5] (1937) of both prolan and pituitary extracts the results were essentially negative in 79 cases. Campbell and Sevringhaus[6] (1939) reported some successes and failures with a few selected representative cases. They found it very evident that more potent and more purified hypophyseal preparations were needed.

In 1930, Cole and Hart[7] reported the very potent gonadotropic effect of pregnant mare's serum on the ovaries of rats. Other excellent papers on the experimental study of mare's serum hormone have appeared by Goss and Cole[8] (1931), Cole and Miller[9] (1933), Catchpole and

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*From the Department of Obstetrics and Gynecology, University of Louisville School of Medicine.

Lyons[10] (1934), and Cole and Sanders[11] (1935). This material is present in the blood of mares in very high concentration from the fiftieth to the one hundredth day of pregnancy. It rarely appears in the smallest amount in the urine, possibly because of its high molecular weight. It will not dialyze, while prolan does easily. It will bring about maturation of follicles, estrus, ovulation and the development of corpora lutea in the rat, mouse, sow, cow and ewe. After hypophysectomy it stimulates the ovaries very much more effectively than prolan. In spite of the differences from human pregnancy urine hormone and certain similarities with the hypophyseal hormone, there is some evidence pointing to its origin in the mare's placenta.

Because separation of this material from mare's blood was difficult, the study of the hormone in women was retarded. Following the researches of Gustus, Meyer and Woods[12] (1936) and Cartland and Nelson[13 14] (1937, 1938), the hormone has been prepared largely free of serum proteins and standardized by the weight increase of ovaries of rats. It is now offered by several commercial companies either in solution or in the dry form. The latter is said to be preferable because of its loss of potency if kept in solution.

The use of pregnant mare's serum hormone clinically was very briefly reported by Bowes[15] in 1937. Of five cases of amenorrhea or oligomenorrhea, four were regulated. In one case an endometrial biopsy after treatment showed a secretory phase. Frank, Goldberger, Salmon and Felshen[16] (1937) very briefly mentioned that four cases of amenorrhea failed to respond to this hormone.

In 1938, Davis and Koff[17] presented a most striking article on this subject, claiming the production of ovulation for the first time in the human by giving pregnant mare's serum hormone intravenously. Thirty-six women at various stages of the menstrual cycle were given from 50 to 70 units of "gonadogen" intravenously 16 to 76 hours before operation. Sixteen of the cases had young corpora lutea. There has been some criticism of this work, because at least five of the cases had their fresh ovulations between the tenth and sixteenth day of the cycles, a time when they might very normally occur. It is also difficult to interpret some of the endometrial findings.

Hartman,[18] in 1938, performed 104 experiments on monkeys, using "gonadogen." In 32, there was little or no response in the ovaries. In 5 there was normal follicular enlargement only. In 16 there was diffuse over-stimulation of the ovaries with the formation of multiple follicular cysts. In 28, ovulation occurred, but more careful examination indicated that 5 ovulated before injection and 16 might have ovulated anyway. There were 7 unequivocal cases that did ovulate apparently from the hormone. This paper is particularly important in indicating that ovulation may be brought about in some cases, that a certain dose may stimulate one animal and not another, and that over-stimulation may produce multiple follicular cysts, which regress after a period of time.

In 1939, three clinical articles appeared. Kennedy and Shelton[19] reported 10 cases with periods every 2 to 3 months or amenorrhea of 2 to 24 months' duration, treated with 50 units of "gonadogen" each month. Nine of the ten were regulated. In three additional cases with menorrhagia, apparent clinical cure was obtained in two. Hall[20] reported the use of "gonadin" in 135 cases. Of the cases with menstrual disturbances, 58 per cent were cured; genital hypoplasia, 47 per cent were cured; and sterility, 55.8 per cent were cured. This report is so brief as to give practically no details. It is merely stated that 24 of 43 cases of sterility conceived after receiving this hormone. There is no evaluation of treatment to the cervix, biopsy of the endometrium, or Rubin's test. One is led to presume that 55.8 per cent of cases with sterility, at least in that series, were due to failure of ovulation. In our opinion sterility due to failure of ovulation in a woman with normal, regular menstrual periods is a distinct rarity. We cannot see any proof that ovulation and pregnancy were caused by this hormone in these cases. Rubinstein[21] studied 35 cases of sterility and determined by means of basal body temperatures and vaginal smears that 19 did not ovulate. Twelve of these were given "gonadogen." Six gave evidence of ovulation by the above methods and 4 became pregnant. The accuracy of these methods for determining ovulation is still unproven, as evidenced by finding 19 anovulatory out of 35 cases.

The work of Davis and Koff suggested that pregnant mare's serum hormone will stimulate the human ovary to ovulation. Careful observations should be made to avoid the mistake of over-enthusiasm, which occurred with the human pregnancy urine preparations. While the reports of purely clinical results are important,

enthusiasm and small groups of cases may lead us astray. Even if the hormone is effective in producing ovulation in the normal ovary, its real value is in producing a similar reaction on the abnormal ovary in hormonal dyscrasias. We have attempted to study the effect of this hormone on the abnormal ovary as evidenced by endometrial biopsy, assuming that the endometrium reflects the state of the ovary. We have used only the product "gonadogen,"* as prepared by Cartland and Nelson.

In this series there are 33 cases, 11 with amenorrhea, 7 with endometrial hyperplasia, 7 with interval non-secretory endometrium which we believe should be considered in the hyperplasia group, but probably having less hyperestrinism, 2 with secretory endometrium, and 6 with metrorrhagia in which biopsies were not taken.

The 11 cases of amenorrhea were all of the secondary type, having menstruated at least from four months to three years previously, usually preceded by oligomenorrhea. Their ages varied from 17 to 28 years. Endometrial biopsies were taken on two or more occasions before treatment in all but one case. Seven showed interval non-secretory endometrium only fairly well developed, two definitely atrophic endometrium, and one well developed non-secretory endometrium with "Swiss cheese" glands. These patients were treated from one to sixteen months with a total of from 30 to 710 units each. One patient developed marked local reactions from four subcutaneous injections and treatment was discontinued. Of the remaining ten, eight menstruated, seven regularly or fairly so. Repeated biopsies showed the gradual development of a premenstrual secretory endometrium, proven in 4 cases after from two to thirteen months' treatment. In two cases with regular menstruation follow-up biopsy was not obtained. One with two normal periods to date still has a non-secretory endometrium. One failure has had only 30 units of treatment, obviously insufficient. The other two complete failures have been followed for nine and twelve months with biopsies and 30 to 90 units of "gonadogen" every month. The hormone was given either intramuscularly or intravenously. The one case has had a resting stage endometrium of non-secretory type on every occasion. The second case had an atrophic endometrium in the beginning, with slight growth effect for five months, after which the endometrium became very atrophic. These two cases are apparently refractory to the hormone.

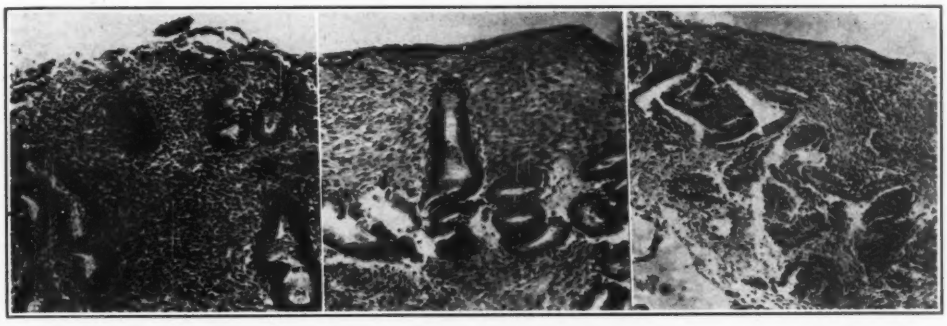
*For a generous supply of "gonadogen" we are indebted to the Medical Research Division of the Upjohn Company.

Table 1

AMENORRHEA

Case	Age	Duration	Endometrium	Mare's Serum	Observation	Clinical Result	Follow-up Endometrium
1	18	3 yrs.	Atrophic	350 units	12 mos.	Scant period third month. None later for 9 mos.	Atrophic
2	19	6 mos.	Atrophic	260 units	12 mos.	Regular menses for 9 mos.	Premenstrual, after 6 mos.
3	21	13 mos.	Interval non-secretory	710 units	9 mos.	No bleeding	Interval non-secretory
4	24	9 mos.	Interval non-secretory	100 units	6 mos.	Regular menses for 5 mos.	
5	26	5 mos.	Interval non-secretory	70 units	12 mos.	Missed 2 periods in 9 mos.	Premenstrual 42 days later; recently non-secretory
6	23	14 mos.	Interval non-secretory	660 units	17 mos.	Normal, regular for 12 mos.	Premenstrual after 13 mos.
7	23	6-10 mos.	Interval non-secretory	120 units	5 mos.	Normal, regular	Premenstrual after first treatment; later interval non-secretory
8	18	8 mos.	Hyperplasia	220 units	5 mos.	Regular menses for 2 mos.	Interval non-secretory
9	17	4 mos.		110 units	2 mos.	Menses in 6 weeks	
10	25	8 mos.	Interval non-secretory	30 units	17 mos.	Amenorrhea for 14 mos., followed by 3 regular menses	Interval non-secretory
11	28	20 mos.	Interval non-secretory	40 units	5 mos.	Local reaction; 1 menses 3 mos.	

The second case with atrophy, then stimulation followed by atrophy, suggests that an antihormone may have developed. This condition has been studied by Meyer and Wolfe[22] in the monkey. If the hormone were discontinued for a time this refractoriness might disappear, as shown in the monkey. In summary, of eleven cases treated, two very insufficiently, eight menstruated, seven regularly or fairly so, and secretory or ovulatory endometrium was proven in

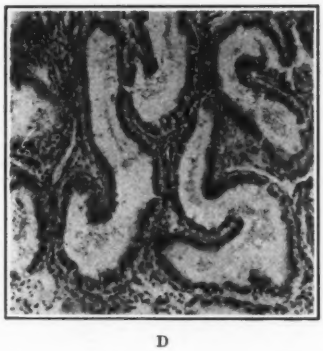


A B C

Case 1. Amenorrhea three years.

A. Twenty-one days after thirty units "gonadogen," interval non-secretory.
B. After three months and one hundred and seventy units, interval non-secretory.
C. After two hundred and ten units, atrophic non-secretory.

A B C



D

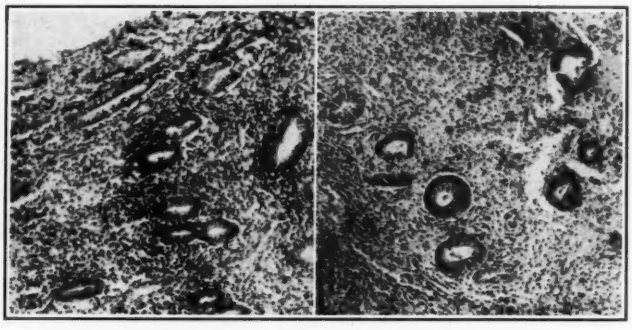
Case 2. Amenorrhea six months.

A. Before treatment, non-secretory.
B. Twenty-six days after forty units "gonadogen," late interval, secretory.
C. One day before period, three months since last "gonadogen," total dose one hundred and seventy units, interval non-secretory.
D. Fourteen days after thirty units, two days before menses, late interval secretory.

Fig. 1

at least four. In two cases, continued treatment was necessary from 6 to 10 months after menstruation began before a premenstrual secretory endometrium was obtained.

There were seven cases of endometrial hyperplasia, showing overgrowth of the endometrium, no secretion, and a "Swiss cheese" pattern of the glands. These cases all had irregular, profuse or prolonged menses. All but one had a very well developed uterus. Two or three biopsies were taken before treatment and repeated every two to four weeks thereafter. These patients were treated from one to sixteen months



A B

Case 3. Amenorrhea thirteen months.

A. Before treatment. Interval non-secretory.

B. After ten months and six hundred and forty units "gonadogen," same.

A B C

D

Case 7. Amenorrhea six to ten months.

A. Before treatment. Interval non-secretory.

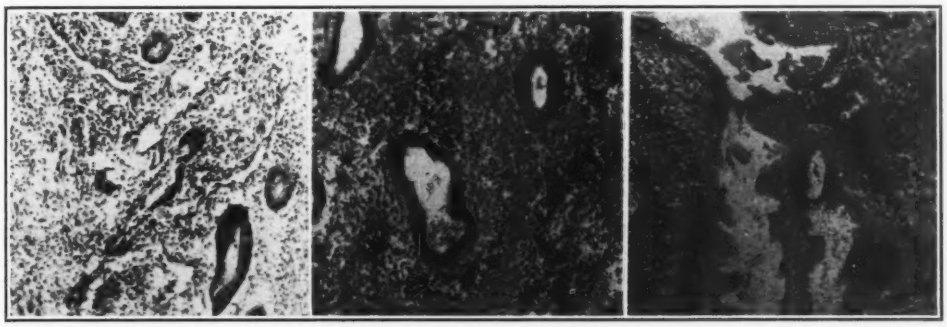
B. Fourteen days after sixty units "gonadogen." Interval non-secretory.

C. Thirty-five days after sixty units "gonadogen," premenstrual. Menses next day.

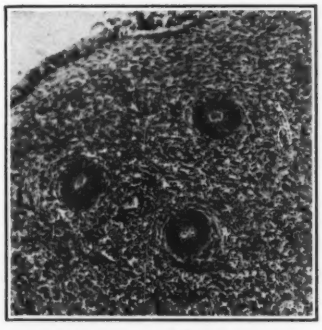
D. Last "gonadogen" three months ago, menses regular, interval non-secretory.

Fig 2

with a total of 60 to 350 units. At times the bleeding seemed to be checked temporarily only to recur shortly. More frequently there was no effect on the bleeding. The endometrium was not changed except in one case where a premenstrual endometrium was obtained. This patient was 43, the only older one in the group. Her menorrhagia persisted; hysterectomy showed a small submucous myoma. In these seven cases, five were proven to have had no endometrial



A B C



D

Case 5. Amenorrhea five months.

A. Before treatment, interval non-secretory.

B. Twenty-eight days after forty units "gonadogen," very early secretion.

C. Forty-two days after "B" and thirty units "gonadogen," premenstrual, followed by first menses.

D. Four days before fourth period, non-secretory.

A B C

Case 6. Amenorrhea fourteen months.

A. Before treatment. Non-secretory, atrophic.

B. Nine days after thirty units "gonadogen." Late interval secretory.

C. After thirteen month's continued treatment, premenstrual.

Fig. 3

change, although one of 20 years of age has had normally recurring periods for 6 months after four years of marked irregularity. Her uterus was rather small.

There were seven cases of metrorrhagia with interval non-secretory endometrium. These, we believe, are very closely akin to the above group of hyperplasia, although probably having less hyperestrinism. Their ages varied from 15 to 29 years. They were treated with from 60 to 330 units. Two patients developed essentially normal menstruation, one was improved for 3 months to relapse, and three were definitely unimproved. Three developed slight secretion in the endometrium, and one developed a normal premenstrual endometrium. While three patients developed slight secretion and one a full secretory effect, only two were clinically cured and one of these had an anovulatory endometrium when last seen.

There were two patients with irregular bleeding and a secretory endometrium. They were treated with 60 and 250 units. The latter developed a markedly decidual-like endometrium. In neither, however, was there any very definite effect upon the bleeding.

There were six cases with relatively minor derangements in all but one. Biopsies were taken in none of these. They were treated with from 30 to 120 units of "gonadogen." One with quite small uterus who had bled irregularly for 11 years, has had normal regular periods for 6 months after 60 units. Attempts at biopsy were unsuccessful because of the small cervical canal. The others have all been improved or regulated. As stated above, the summary of this group of clinical cases with minor derangements is of some value, but we do not presume that we have proven anything in this group. The natural

Table 2

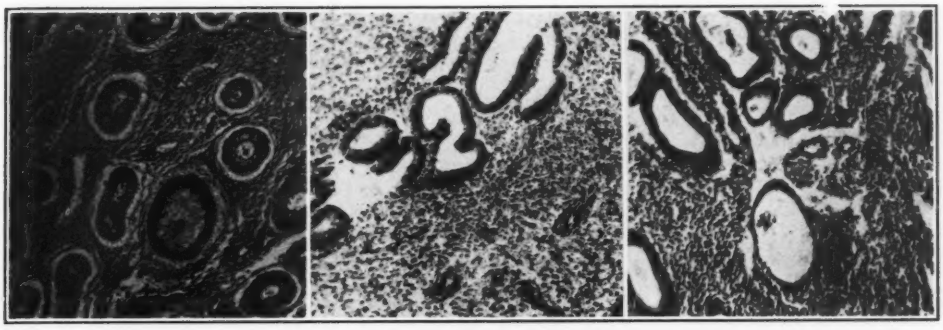
ENDOMETRIAL HYPERPLASIA

Case	Age	Duration Metrorrhagia	Mare's Serum Units	Observation	Clinical Result	Follow-up Endometrium
12	20	4 years	200	6 mos.	Regular menses for 5 months	Same before second menses
13	25	8 years	260	16 mos.	Unimproved	Same
14	23	2 years	350	6 mos.	Slightly improved	Same
15	18	5 years	140	2 mos.	Unimproved	Same
16	25	4 mos.	90	1 mo.	Unimproved	Same
17	43	2 years	120	6 mos.	Menorrhagia, hysterectomy, submucous myoma	Premenstrual
18	23	5 years	60			

Table 3

METRORRHAGIA WITH INTERVAL NON-SECRETORY ENDOMETRIUM

Case	Age	Duration	Mare's Serum Units	Observation	Clinical Result	Follow-up Endometrium
19	18	3 mos.	60	6 mos.	Regular menses	Same
20	16	4 years	200	6 mos.	3 mos. normal; bled 25 days; irregular	Late interval secretory, followed by non-secretory
21	22	2½ mos.	30	14 mos.	Regular; slight menorrhagia	Premenstrual
22	18	3 years	140	12 mos.	Slightly improved	Late interval secretory
23	29	18 mos.	330	6 mos.	Unimproved	Same
24	15	1 year	60			
25	29	8 mos.	150	2 mos.	Unimproved until thorough curettage	Late interval secretory



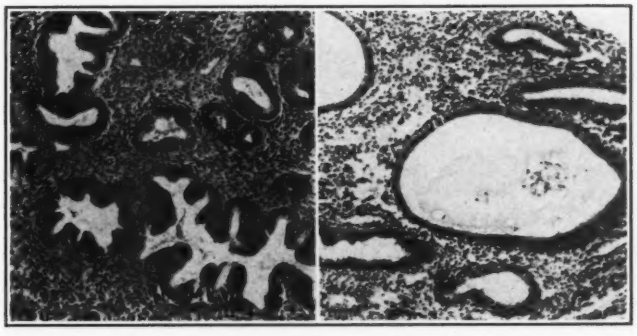
A B C

Case 13. Endometrial hyperplasia.

A. Before treatment. Hyperplasia.

B. After two hundred units "gonadogen," hyperplasia.

C. After two hundred and fifty units "gonadogen" in six months, hyperplasia.



A B

Case 14. Endometrial hyperplasia.

A. Before treatment, hyperplasia, non-secretory.

B. After six months and three hundred and twenty units, hyperplasia, non-secretory.

Fig. 4

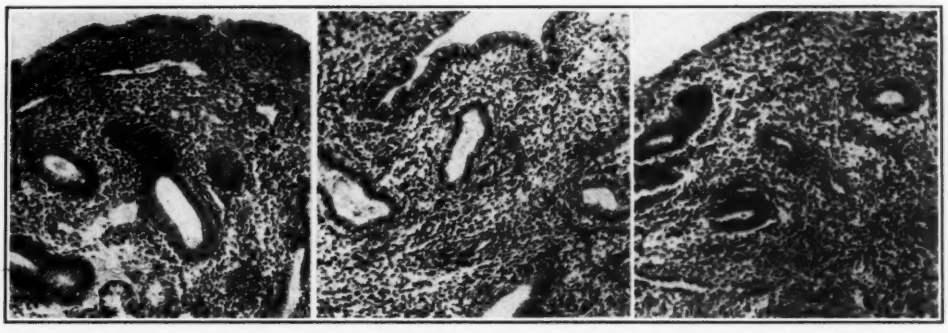
Table 4

METRORRHAGIA WITH PREMENSTRUAL ENDOMETRIUM

Case	Age	Duration	Mare's Serum Units	Observation	Clinical Result	Follow-up Endometrium
26	20	6 mos.	250	3 months	Slightly improved	Decidua-like
27	29	10 mos.	60	6 months	Unimproved	Late interval secretory

METRORRHAGIA WITHOUT BIOPSY

Case	Age	Duration	Mare's Serum Units	Observation	Clinical Result
28	13	4 months	70	1 month	Improved
29	24	1 month	30	2 months	Improved
30	26	3 months	60	3 months	Improved
31	32	5 months	120	2 months	Improved?
32	25	1 month	30	3 months	Improved
33	26	11 years	60	6 months	Regular menses



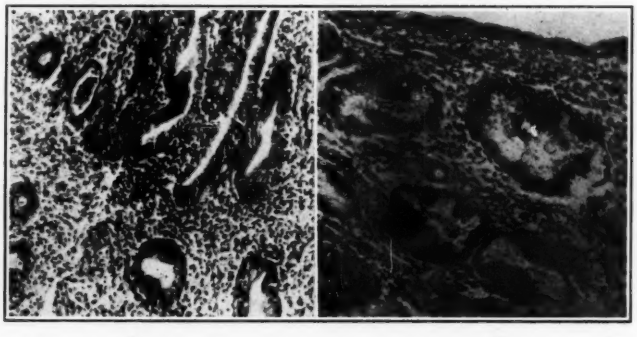
A B C

Case 20. Metrorrhagia four years.

A. Before treatment, interval non-secretory.

B. After thirty-five days and sixty units "gonadogen," late interval secretory.

C. Two months after last "gonadogen," day before menses, interval non-secretory. Metrorrhagia.



A B

Case 21. Metrorrhagia two and a half months.

A. Before treatment, interval non-secretory.

B. After seven days and thirty units "gonadogen," premenstrual.

Fig. 5

tendency for women to revert to normal cycles may obscure the interpretations.

In this study we have used "gonadogen," prepared in 10 unit tablets in individual sterile vials, which are dissolved in sterile solution when used. The dry form maintains the potency which may be lost over a period of time in solution. Patients are probably best tested for horse serum sensitivity by placing a drop of the solution in the conjunctiva. There is evidently very little serum protein in the material. One of our patients developed red wheals after subcutaneous injections, but had no reactions from repeated intravenous injections. One patient developed a large red nodule at the point of injection and fainted. Another felt faint and had a sensation of choking during an intravenous injection. No further reactions occurred in the series after very numerous injections. The dosages varied. Some patients received 10 units daily for 6 days subcutaneously, 10 units subcutaneously for 3 days followed by 30 units intravenously, or 40 to 80 units intravenously. We rather favored the second method. In amenorrhea the treatment was repeated every 28 days. In other cases the treatment was given between the sixth and twelfth day of the cycle if it could be determined.

Other investigators have shown that very probably the pregnant mare's serum hormone will produce ovulation in normal ovaries in 50 per cent of cases. In our study by the indirect

method of obtaining endometrial specimens it seems that the ovary in amenorrhea may be stimulated not only to bring on cyclic bleeding, but if continued, to produce ovulation, corpus luteum formation and secretion in the endometrium in the majority of the cases. Of bleeding cases of the anovulatory type with assumed follicular cysts, the majority did not respond. Apparently the cysts will not ovulate following use of the hormone as we have employed it. These ovaries, already over-stimulated, are apparently not helped by further stimulation in this manner. It does seem possible that bleeding cases with underdeveloped uteri may be helped by this hormone. Careful scientific studies using various dosages are indicated both in fairness to this hormone and to future patients.

SUMMARY

(1) The effect of pregnant mare's serum hormone in the form of "gonadogen" was studied by endometrial biopsy in thirty-three cases of apparently abnormal ovarian secretion.

(2) Of eleven cases of amenorrhea treated from one to sixteen months, eight menstruated, seven regularly or fairly so. A gradually developing premenstrual secretory endometrium was proven in at least four cases. Two cases were apparently refractory and two were insufficiently treated.

(3) Of seven cases of endometrial hyperplasia with metrorrhagia, a secretory endometrium was obtained in the one middle-aged case. Only one of the six younger patients was clinically regulated.

(4) Of seven cases with interval non-secretory endometrium and metrorrhagia, three developed slight secretion and one a normal premenstrual endometrium. Only two were clinically cured.

(5) Two cases with secretory endometrium and metrorrhagia were not improved.

(6) Six cases, all with minor metrorrhagia, but one, in which no biopsies were taken, were improved or cured.

(7) The pregnant mare's serum hormone will apparently often stimulate the abnormal ovary where there is subnormal stimulation, as in amenorrhea and oligomenorrhea. It is possibly of value in metrorrhagia where the uterus is small.*

*We are indebted to Dr. A. J. Miller for his complete cooperation in the Department of Pathology, and to Miss Dorothy Blumer and Mr. O. M. Alton for their technical assistance.

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DISCUSSION (*Abstract*)

Dr. Quitman U. Newell, St. Louis, Mo.—The hormone in pregnant mare's serum is a discovery of nine years ago, and experimental work has been going on carefully and progressively to standardize it and make it safe for human use. It is now absolutely safe and is given to us in solution for intravenous use, and in tablets, easily soluble in water, for intramuscular use. Dr. Gray has reported his results with it in 33 cases, 11 with amenorrhea, 14 with endometrial hyperplasia, 2 with secretory endometrium, and 6 with metrorrhagia. His results have been fairly satisfactory, but it has not been infallible. He has studied all of these cases carefully and has called our attention to the care with which this gonadotropic hormone should be used. He is to be congratulated on this fine piece of work.

We now believe that the anterior lobe of the pituitary gland is responsible for two distinct reactions in the control of ovarian function. The first is a follicle-stimulating hormone, such as that obtained from the urine of women in the postmenopausal period. Under the influence of the "follicle stimulator" primary follicles grow to maturity. The second factor is a luteinizing hormone. Ovulation and the conversion of the follicle cavity into a corpus luteum depend on the concurrent action of these two fractions at a proper stage in follicle development. A pure luteinizer has not been isolated as yet, but the gonadotropic hormone in pregnancy urine comes the nearest to being a pure luteinizer.

Ovulation in the human being probably is the result of a proper balancing of these two actions. There is little evidence at present to suggest the existence of an ovulation center. In the human being the entire ovulatory mechanism is under endocrine control, although in non-spontaneously ovulating animals nervous stimuli probably start the mechanism for the production of ovulation.

It has been a relatively simple procedure to produce ovulation experimentally in most laboratory animals. In non-spontaneously ovulating types, ovulation can be induced by the injection of most gonadotropic principles.

Ross and Hamblen have shown that gonadotropic substances derived from pregnancy urine and blood when given parenterally have failed to produce any consistent changes in ovarian activity. Davis and Koff, using a single intravenous injection of 50 to 60 units of this hormone, have been able to produce experimental ovulation in normal women within 24 to 36 hours.

The gonadotropic hormone found in pregnant mare's serum is definitely different from preparations of urinary prolan. Unlike gonadotropic substances in the blood and urine of pregnant women, the mare's serum fraction is not excreted in the urine at any time during gestation. It is not ultrafiltrable through collodion membranes as are pregnancy urine substances. The mare's serum hormone either has a higher molecular weight or possibly is combined with a large molecule which prevents it from passing through collodion membranes.

The apparently proper indications for the use of this new and valuable hormone are amenorrhea, menorrhagia and sterility. Amenorrhea of short duration certainly offers the greatest per cent of cures. Cases of long standing are best treated by the addition of small doses of thyroid. Cases of menorrhagia are less favorable.

Some show immediate response to treatment with the hormone, while in other cases the number of days of bleeding is cut down temporarily, but does not settle down to a five-seven day period. They also require prolonged monthly treatment. Cures in cases of sterility I am afraid are over-estimated, some authors reporting 55 to 57 per cent. To me these figures are rather high, and admitting its value in stimulating ovulation and a good egg output, I do not believe the endocrine cause of sterility is so great as do some investigators.

We must not be overenthusiastic in the use of this comparatively new hormone. It seems to be the ideal hormone to produce ovulation in selected cases, as it apparently possesses the two necessary factors, estrin and progestin. We must not forget the fundamentals of this hormone, and must classify the patients on whom we are going to use it very carefully, or it will very rapidly fall into disrepute, as has the hormone obtained from the urine and blood of pregnant women. In the use of the gonadotropic hormone, it has been shown that large doses stimulate atretic follicle formation in the ovaries without ovulation. Then is it not possible if these large doses are continued to produce malignancy of the organs of the generative tract? I wish I had time to discuss some of the hormone theories of malignancies of reproductive organs. We must feel our way before we claim too much for this hormone and be very careful in our administration of it.

Dr. Gray (closing).—We feel that this hormone is one of the most important yet discovered, but we should be careful and should do control investigations instead of making the errors we made with the prolan preparations. Our work is just a beginning of what should be done with this material. It seems to me that it is of considerable value in amenorrhea and in developing small uteri. It may be of value in dysmenorrhea with small uteri, but in the majority of bleeding cases in our opinion it is of very little value.

THE STATUS OF RETROBULBAR NEURITIS IN PARANASAL SINUS DISEASE*

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The association of lesions of the optic nerve with suppuration or hyperplastic disease of the posterior group of nasal sinuses is a logical premise when we consider that the nerve in 75 per cent of cases passes through the upper and outer anterior part of the sphenoid sinus. In this course it is very shallow, the bony covering is very thin, and sometimes absent (Onodi[1]). At times it is found most superficial in the ethmoid cell adjacent to the sphenoid. Thus the absorption of pus from a primary inflammation and the pressure effect from hyperplastic membranes have an easy, direct effect on the nerve, appearing to establish a direct etiologic relationship. The features of wide variation in size and disposition of the sphenoid cells as demonstrated in x-ray study and at operation invariably appear as the chief point of interest when a group of cases are being studied in connection with optic neuritis. It has been assumed, in cases in which the eye lesion recovers quickly after the resection of the posterior sinuses that the process is one of (a) drainage of infectious material away from intimate contact with the optic nerve; (b) decompression of the nerve by free incision of many adjacent blood and lymphatic vessels; (c) relief from direct pressure by engorged membranes and by another reasoning; (d) production of hyperemia, which restores the blood supply to the nerve which has been lost in the pressure effects from swelling within the bony canal or in thrombosis of the small vessels supplying it.

Berger and Tyrmann[2] reported twenty-six cases in 1886.

Fliess,[3] in 1893, reported a case relieved by opening the sinuses. In the period from about 1908 to 1915 great numbers of the cases appeared in the literature, ascribing retrobulbar neuritis to sinus disease, and lesions of the optic nerve secondary to sinusitis were considered common, percentages being given by various authors

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varying up to 17. Toxic sources of optic neuritis such as tobacco, alcohol, chemicals, and constitutional diseases as diabetes, lues, rheumatism, pellagra, tumor, were all accountable and accepted.

Hajek,[4] in 1912, reported one of the earlier cases improved by an endonasal procedure, in which a relapse two years later proved it to be multiple sclerosis. The general symptoms were entirely latent at the time of operation. The improvement in these cases was explained as relief of some vague inflammatory process in the medullary spaces of the bone surrounding the optic nerve. Hajek later revised the incidence of sinus disease etiology downward in view of the common finding of multiple sclerosis. Beck and others reported similar cases.

Sluder, Sauer, Loeb and associated ophthalmologists recorded with painstaking care many excellent examples in the decade following 1908. Following reports of entirely spontaneous recovery of retrobulbar neuritis by Mollison, Von Gilse and Hajek, around 1915, Thoma stated in open meeting that at least 90 per cent of all cases would recover.

L. White,[5] in 1928, in exhaustive studies on the subject, concluded that other foci such as teeth, tonsils and distant lesions, have more to do with the neuritis than sinuses; this replaced his previous theory that when sinuses were at fault it was a negative pressure effect within the sinus, favoring emigration of toxins and bacteria to the district of the close lying optic nerve.

Gradle,[6] in 1915, described an interesting anatomical theory as to the production of central scotoma by involvement of the central vein of Vossius secondary to involvement of the periostial or dural veins next to the sinuses by continuity.

Oliver and Crowe,[7] in 1927, reported ten thoroughly studied cases in which the cause of optic neuritis clearly seemed to be infection of the nasal sinuses. Microscopic sections of tissue removed from posterior ethmoid cells showed myxomatous degeneration and cellular infiltration of the mucous membrane.

McMahon,[8] in a previous study, had described these changes, as well as bone changes, fibrosis, hyperostosis, osteomalacia and necrosis, in pathologic changes occurring in spheno-ethmoid sinusitis.

Benedict,[9] in 1933, recognized and confirmed by therapy the theory that interruption of function of the optic nerve, producing central or peripheral scotoma, results from direct pressure on the nerve by tumors on the nerve or its sheath, adjacent to the chiasm, the pressure interfering with the blood supply of the nerve, as is seen in pallor of the optic disc, a characteristic finding in tumor of the pituitary gland. He reasoned that because toxic effects were carried to the nerve by the circulation, the improvement of the nerve after operation was due to improvement in circulation of the nerve. On this basis he felt that the same intranasal effect could be accomplished by use of 2 per cent solution of iodine on the nasal mucosa and improvement of the peripheral circulation by vasodilating agents such as nitrites or pilocarpine. Analyzing 225 cases of retrobulbar neuritis examined in the Mayo Clinic, 155 were found to be due to multiple sclerosis and the remainder to various toxic effects, with only one case claimed by sinus disease. In 500 cases of proven multiple sclerosis, 60 per cent had had intranasal sinus operations performed elsewhere. Conceding the rhinogenic origin of at least an occasional case, he decried the use of any sinus operation for the relief of retrobulbar neuritis unless actual suppurative disease could be shown.

Lillie,[10] in 1934, reviewed the same series and relegated the infection of the sinuses to an unimportant place in disturbances of the optic nerve. The estimate as to rhinogenic origin ascribed by various authors and quoted by Campbell[11] in 1936 were: Wilmer, 11 per cent; Langerbeck, 3.5 per cent; Walker, 5 per cent; Scheerer, 1.5 per cent. Campbell also observed the scarcity of retrobulbar and optic neuritis in children and considered it significant in view of the greater frequency of sinus infection in young children as compared with the incidence in adults. He considered this an argument against direct extension of sinus infection to the optic nerve with the possible exception as follows: that in view of the anatomical proof by White[12] that the diameter of the optic canal in young children is the same as in the adult, considerable swelling of the proportionately smaller optic nerve of the child could occur before it would be subjected to pressure. Taking a very conservative stand, he conceded, even in the face of his comprehensive review of the large number of discouraging opinions, that there really is an occasional indication for surgical drainage of the sinuses in retrobulbar neuritis.

The most recent comment on this relationship has come from a neurological service (Strauss and Needles[13]) reporting favorable reactions of

retrobulbar neuritis cases to sinus drainage. Even in cases which later proved to be multiple sclerosis, the surgery was still claimed to be indicated.

There is general agreement, as noted by Gill,[14] in the association of chronic posterior uveitis with foci, tonsils, sinuses, teeth and the lower colon, and that every corrective treatment should be used.

Following are the brief records of thirteen patients whose visual disturbances were suspected to be due largely to absorption from toxic foci about the nasal sinuses. The most important conclusion which may be drawn simply indicates the preponderance of lesions of the retina and choroid which respond to surgical drainage of the sinuses rather than retrobulbar neuritis.

Case 1.—R. L., aged 29, was seen August 1, 1932. For a number of years this patient was aware of some disturbance in the left eye, but was not examined even when two years previou ly he had failure of both eyes, lasting a few days with recovery. He ascribed the blurring to medication for a general ailment and remained in bed. Six months before, he consulted an ophthalmologist because of vertex and supra-orbital headache, but nothing was found. Two weeks before, after increase of headache, his left eye blurred, and one week before the right blurred as well. The condition was diagnosed acute chorioretinitis and complete physical examination, including serological studies, was made. All tests were negative.

On July 26, 1932, the nose was entirely negative as to evidence of infection. Three days later while he was being observed, sterile saline was displaced into the posterior sinuses, producing a large quantity of heavy yellow pus. X-ray study showed sphenoid involvement and opacity of the right antrum. The vision was 20/100 in the right eye and 10/200 in the left. On August 1, 1932, both sphenoids and all posterior ethmoids were resected and an intranasal window made into the right antrum. Recovery of the eyes was prompt, with vision practically normal fifteen days after the sinus operation. To this date there is no sign of multiple sclerosis.

Case 2.—C. C., aged 22, seen March 18, 1933, had habitual headache, chorioretinitis and astigmatism of the right eye diagnosed in 1932. There was no other trouble until blurring and loss of vision in the left eye began three days earlier following a cold. Regular vertex and supra-orbital headache had been habitual in the preceding year. The patient was referred on this date with a diagnosis of chorioretinitis left, vision 6/20, left eye, large vitreous floaters and disc margins blurred.

Examination of the nose showed a purulent sphenoiditis on the left side with thickening of the plica septi, which suggested a chronic sphenoiditis of long standing. General examination was entirely negative. On March 21, 1933, the left sphenoid and posterior ethmoids were resected. The sphenoid was extremely large and encroached across the midline on the position usually occupied by the right sphenoid. The first improvement was noted after ten days, and definite improvement in six weeks. A partial central scotoma remained. On March 27 the vision was 6/7.5 partly, and on May 17 it was 6/6 partly. Headaches were improved.

Case 3.—C. S. N., aged 32, seen February 10, 1932, had noted blurring of the right eye slowly for two years, attributed to gazing steadily at market charts. General examination was negative. Chorioretinitis and possibly optic neuritis in the right eye had been diagnosed. There was no evidence of sinus infection. Septic tonsils were removed February 16, 1932, with prompt improvement of eye symptoms, which were clear in two weeks. On November 21, 1934, he had a similar attack in the left eye. Hemorrhagic retinitis was diagnosed by the ophthalmologist. The patient is a heavy user of alcohol and tobacco.

On this date there was evidence of chronic infection about the posterior sinuses, the mucosa covering the sphenoid district being thickened and bearing dark engorged blood vessels. X-ray study suggested an old infection in all the posterior cells. He was referred to the hospital and the left sphenoid group of sinuses were resected. A large polyp was removed from the cavity of the sphenoid. The vision in the left eye slowly improved and on May 8, 1936, examination showed visual acuity (R) 6/15.2, (L) 2/30-2/20, a reduction from his previous improvement after a severe nasal infection. He was sent to the hospital and webbing, which had completely covered the field of his sinus operation, was removed. Partial recovery of the left eye followed, with a permanent central scotoma. He has been under observation since and his vision improves at times and loses ground at others. A typical reading will show, as on May 26, 1938 (R) 20/48 and (L) 20/192. It is to be noted that the right eye remains unchanged and carries an old retinal scar from a lesion some years before.

Case 4.—C. C., aged 30, September 23, 1936, had acute chorioretinitis, left and right, and vision (R) 5/20 and (L) 5/20. The attack was preceded two weeks before by a mild pharyngitis and intensely painful irritation of all branches of the V nerve on the right side. A deviated septum occluded the left nasal space and x-ray study showed cloudy maxillaries. There were no other signs of infection present.

On September 26, 1936, septum deviation was corrected and intranasal windows were placed in each antrum. Polypoid tissue was removed from the left antrum. Both eyes recovered rapidly and on October 2, 1936, the vision was 15/13 R and L.

Case 5.—Mrs. O. A. C., aged 30, February 7, 1934, was two months postpartum and since delivery had a heavy postnasal discharge of clear mucopus. On the above date she complained of blurring vision and was found to have an optic neuritis in the left eye, with vision of 3/80. Displacement with sterile saline produced large quantities of pus about the posterior sinus recesses.

Surgical drainage of the sinuses was advised, but the patient refused, and displacement treatment was continued on alternating days. The eye lesion slowly improved. Vision on February 10, 1934, was 6/80 and on February 27, 1934, was 6/7.5 partly. On September 4, 1934, it was 6/6-1.

Case 6.—Mr. H. K., aged 41, a carpenter, was seen September 25, 1935. In his work he was much exposed to cold and after a severe sore throat one week before

the above date he developed blurred vision. His condition was diagnosed hemorrhagic retinitis and his visual acuity as reported was 5/100 in the left eye. Fresh pus was observed about the left sphenoid district and heavy pus was washed from the left maxillary sinus.

On September 26, 1935, the spheno-ethmoid sinuses on the left side were resected and window drainage was made in the left antrum. The eye promptly recovered with complete disappearance of the lesion in two weeks. On October 1, 1936, the vision again blurred after a severe cold, with appearance of hemorrhagic retinitis in the left side and vision for this eye of 5/80. Webbing was removed from the region of the left posterior cells and the eye again recovered with vision on October 1, 1938, as 6/6-2.

Case 7.—Mrs. A. G., aged 78, seen September 5, 1935, had lost the vision of her left eye from glaucoma and cataract in 1926. Acute chorioretinitis was observed on the right side for one month past. Fresh pus draining from the maxillary sinuses on this examination was removed by irrigation of the antra by the natural ostia. The eye was slightly improved, but surgical interference about the sinuses was considered too hazardous, in view of her hypertension and arteriosclerosis. After one month a large central scotoma remained.

Case 8.—Mr. J. L. D., aged 23, seen October 7, 1935, had a blurring of the right eye for nine years, but no effort had been made to have it treated. A week before the date of this examination, following an active cold, he had a blurring of the left eye which was diagnosed hemorrhagic retinitis of the left side and central choroiditis of the right. Vision (R) was 4/200 and (L) 15/50.

The sinus findings were suggestive but not well defined, and the condition was considered urgent enough for resecting all posterior sinuses on the left side. This was done November 11, 1935. The recovery of the left eye was slow and never satisfactory, leaving an old scar in the left retina similar to that seen on the right. Repeated fever therapy was used. On January 11, 1936, vision was (R) 15/300, (L) 15/75, and on September 15, 1936, (R) 15/75, (L) 15/200.

Case 9.—Mr. S. W. C., aged 24, seen January 14, 1936, had had failing vision of the right eye for one year. Diagnosis at examination was fresh hemorrhage at site of old chorioretinitis. No record was made of visual acuity.

An antrum window was made on the right side with resection of all the posterior sinuses. There was slight improvement of vision at first, but the final result could claim no improvement. All serologic tests were negative. After two years there is still no sign of multiple sclerosis.

Case 10.—Mr. N. L., aged 32, was observed with chorioretinitis in the left eye for a week ending September 25, 1936. There were no physical findings and the sinuses were absolutely clear, but the tonsils were large and septic. The tonsils were removed on the above date with rapid improvement of vision; the left eye was clear in a week.

Case 11.—Mrs. H. L. J., aged 24, was seen March 1, 1938. The day following a walk in the cold along a river bank her vision was blurred so that she could not do needle work. The second day after the walk she could not find her way around the house, and on examination her vision was (R) 20/96, (L) 20/96. The diag-

Fig. 1

Submento-vertex view in Case 11 showing unusual variation of the sphenoid sinuses. In such abnormal variations as these Onodi[1] found the optic nerve superficial within the wall of the adjacent ethmoid cells. Size and shape of the structures were confirmed at operation.

Fig. 2

X-ray study of Case 12, which also shows a wide variation in the right sphenoid (R.S.). The odd disposition of the posterior ethmoid cells demonstrates the possible error of considering the ethmoid (E.) as the sphenoid cell, leaving the sphenoid unopened. The right side was resected in this case, confirming the contour of the sphenoid.

nosis was bilateral chorioretinitis with macular edema so extensive that it was urged to do very promptly any indicated nasal surgery.

Examination of the nose showed all the mucosa about the sphenoid recesses engorged and dark red with small flakes of dry mucopus. There were embedded small tonsil fragments. Complete resection of both posterior sinus groups was done on the date of examination with rapid clearing of vision on the third day, so that she could read sub-headlines in the newspaper. The tonsil fragments were removed at the end of one week. The retinal lesions were clear in twelve days. On April 22, 1938, the vision was (R) 20/19, (L) 20/15.

Case 12.—Mrs. B. S., aged 33, was seen June 22, 1938. She had noticed a spot in the center of vision on the right side in August, 1937. Physical examination was negative and tuberculin injections were used for treatment, without improvement. There were several changes of physicians, with discouragement, and when the right side was involved the patient at first refused nasal study. On the date of examination only a peripheral field of vision remained, right 2/150, eccentric, (L) 20/115.

Only old hyperplasia was noted about the sphenoid mucosa, with tortuous vessels, taken as evidence of chronic hyperplastic sphenoiditis. Without promise of improvement the right spheno-ethmoid cells were resected. The retinal hemorrhage on the right side cleared in two weeks, but a large scar remained. The vision has been progressively worse, reading on June 28, 1939, (R) 20/240, (L) 20/115.

Case 13.—Mrs. J. L. H., aged 37, November 17, 1938, gave a history of headaches since 1930, vertex and supra-orbital. Two weeks previously she noticed blurring of the eyes and her condition was diagnosed hemorrhagic retinitis on the right side. She had been taking eye exercises for a year in an effort to correct her headache. Nasal examination showed old hyperplasia about the sphenoid recesses and antrum irrigation produced heavy pus from the left side.

On November 18, 1938, all the posterior sinuses on the right side were resected and a left antrum window made. Recovery of the right eye was rapid and normal vision was reported in six weeks.

The extremely low incidence of retrobulbar neuritis as a result of sinus disease has been repeatedly shown in voluminous reports, some of which are mentioned above; multiple sclerosis remains without doubt the principal confusing element in establishing the etiology. With perennial regularity, records are published describing relief of retrobulbar neuritis from surgical treatment of the sinuses whether the sinuses are markedly involved or not. When the series percentages of improvement from this source are high, they repeatedly raise the controversial issue of the value of surgical drainage of the sinuses.

Close analysis of groups of cases reported in the medical literature revealed descriptions of eye lesions and their course, which may or may not have been retrobulbar neuritis.

Very few cases in this small series had any evidence of general disease. In *Case 7*, there was a moderate arteriosclerosis and hypertension. *Case 3* was an alcoholic and heavy user of tobacco; however, some improvement of his eye lesion followed removal of webbing and scars which had formed over the sinus cavities left by his first nasal operation.

None of these patients was given the diagnosis of retrobulbar neuritis and the source of reference was from seven different contemporary ophthalmologists. This would seem to corroborate the general assumption that true retrobulbar neuritis rarely has its origin in disease of the paranasal sinuses and simply is not referred for investigation. On the other hand, because of the nature of retrobulbar neuritis, in spontaneous improvement of blurring, it is quite possible that many cases are treated by the rhinologist and the eye lesion never recognized.

Eight of these cases received a diagnosis of chorioretinitis, four were hemorrhagic retinitis, and all responded more or less rapidly to surgical measures, such as drainage of the sinuses, or removal of the tonsils. Only two were treated conservatively by irrigation of sinuses and one of these recovered without permanent injury to the eyes. Secondary atrophic changes must have occurred in the other.

The question arises as to whether terminology applied to the eye lesions reported in the literature of rhinology in connection with nasal surgery has not been loosely applied. If diagnoses of the eye cases were more carefully differentiated as to retrobulbar or retinochoroidal lesions, would it not be possible more clearly to define the rationale of surgical drainage of sinuses in connection with them?

The rapidity with which secondary atrophy proceeds within the optic nerve seems to justify prompt drainage by resection of the sphenoethmoidal group of sinuses, or removal of tonsils and carious teeth. The majority of opinions expressed favor such sinus drainage, on its presumptive clinical value, whether involvement may be shown or not. Excellent theories explain the manner of production of retrobulbar neuritis, but the processes involved in its cure, by surgical or nonsurgical treatment, cannot be entirely reconciled.

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DISCUSSION (*Abstract*)

Dr. Millard F. Arbuckle, St. Louis, Mo.—The longer I study this subject the less I know about it. However, the intimate anatomical relationship between the nerve and the posterior group of ethmoid cells and the sphenoid sinus very probably does increase the danger of nerve injury when acute sinusitis is present. Sometimes chronic sinusitis may cause similar eye disturbances. On this basis, relief of the eye disorder after appropriate treatment of the sinus infection is readily understood, but I have never been able to put any credence in reported cure of eye lesions by operation upon uninfected normal sinuses. Certainly I have not seen any such case and I think reports of that kind are pernicious indeed.

Dr. John J. Shea, Memphis, Tenn.—Consultation between ophthalmologist and rhinologist in these cases may be unsatisfactory because we have not come to a clear understanding of our nomenclature of the cause of sudden blindness. We take as the accepted symptom complexes of retrobulbar neuritis, a loss of the central acuity of vision, fundus change, and a definite scotoma in the field of vision; but when the rhinologist gives his opinion as consultant he cannot be definite.

I have never been able to make up my mind after a consultation whether a particular patient will be improved by operation or not; and in the majority of instances it has been necessary to offer him the advantages of surgery with merely the hope that it will be a success.

These patients should have a very thorough examination, anteriorly and posteriorly, and study with a good 'scope.

The sphenoid and the posterior ethmoid cells may very easily come in contact with the optic nerve.

Dr. Leon White did a great deal of work after the turn of the century upon sinus disease and retrobulbar neuritis, and he designed a method of taking a picture to show the size and shape of the optic nerve.

In order to get a good view of the optic nerve, it is necessary that the optic foramen be thrown in the lower, outer quadrant of the orbital ring. If the optic foramen is thrown in the outer, lower quadrant of the orbital ring, then the size and position of the optic foramen may be accepted as a true delineation of its shape. The only definite pathologic conditions that I know, which one can assure the ophthalmologist will be helped by surgery, are those which result from cysts.

A patient came to Dr. Ellett with a total loss of vision in the right eye and a very distinctive displacement of the middle turbinate. We were convinced that the patient had an ethmoidal cyst. The vision in this eye was for moving objects only. Enucleation of this cyst was rewarded by a return of normal vision.

In the few patients whom I have seen with a total loss of vision, with a definite cyst in the ethmoid, one can usually promise that surgery will be of value. On the other hand, we had a patient last year who went suddenly blind and rhinologically had a nose full of polyps and roentgenologically definite pansinus disease. He was operated upon. On the side where he had a vision of 20/40, we merely removed the polyps, uncapped the ethmoid and did a sphenotomy. On the side where he had loss of vision to moving objects, we did the classical Sluder operation of removing the middle turbinate and resecting the anterior wall of the sphenoid. We removed the wall between the sphenoid and ethmoids as completely as possible and did an exenteration of the ethmoidal cells. This man had a return of vision to 20/60 within a week and we were very hopeful of notable improvement, but suddenly vision in that eye receded, and in spite of all forms of treatment it remained for moving objects.

Rhinologically that patient looked as though his vision could be helped by operation; yet after a thorough removal of pathologic tissue, he still lost his vision.

We have not yet means of obtaining sufficient evidence to say which patient can be helped surgically and which must be treated by the hopeful methods of displacement and general medication.

Dr. B. Y. Alvis, St. Louis, Mo.—Dr. Costen has covered a rather wide variety of ocular diseases. At least this subject applies to almost any disease of the posterior part of the eye, including true retrobulbar neuritis, which might be confined to those cases in which there are no visible changes in the optic disc, and those cases in which there is an inflammation of the visible portion of the optic nerve such as we might call a papillitis, and those cases which involve not only the optic nerve head, but the surrounding retina also.

One of the cases which Dr. Costen cited happened to be seen by me first and referred to him, and it illustrates this last classification. This young man, who had lost the central vision of his right eye some years before, and exhibited in that eye a scar extending from the disc to the optic nerve, had a sudden loss of vision in his left eye, as Dr. Costen related. When I saw him, the optic nerve was swollen and edematous and presented a picture of an optic neuritis, that is, an inflammation of one side, you might say, of the optic nerve itself.

This case progressed until much swelling was seen with the ophthalmoscope in the whole region surrounding the optic nerve. The patient was sent to Barnes Hospital, where he was studied first by Dr. Costen, and then exhaustively by the medical department, and no cause was found for his inflammation other than

the suggestive sinus disease. Opening up the sinuses did not result in very much relief of his symptoms.

Another aspect of this group of cases is represented by the second case Dr. Costen showed in his x-ray slides, which you will recall was entitled "Hanlon." This was operated upon by me for cataract in one eye, with normal vision resulting for some months, followed by a gradual recession of vision in this eye, with no ophthalmologic signs to account for the receding vision. He later found that I was not restoring his vision and went to Dr. Post. Dr. Post referred him to Dr. Costen, who opened the sinuses and, following the opening of the sinuses, I understand from Dr. Post there was considerable improvement in the vision of this eye which, unfortunately for him, was not permanent. This is probably not a true retrobulbar neuritis, and I would suspect from the history that the cause is not known.

Another type is represented by a case I remember very well. I saw the patient recently. Many years ago she was seen in our service with a total loss of vision in one eye without ophthalmologic signs. There was no sign, and no evidence, either, of sinus disease, but in those days we were enthusiastic about sinus disease as the cause of retrobulbar neuritis, and the sinuses were opened, with very prompt restoration of vision to normal, and that vision has remained normal up until this day, which is at least ten or fifteen years later. There is some evidence of pallor of the disc, showing there was a true retrobulbar neuritis.

This case could not be classed as multiple sclerosis, I believe, because no further evidence of change occurred, but must simply be classed as idiopathic retrobulbar neuritis, cause unknown, and the restoration of vision certainly followed the opening of the sinus, whether it was because of the opening of the sinus or not.

Another type of case is illustrated by a patient we had some years ago, very similar to the first one I mentioned, with swelling of the optic nerve, associated with evidence of retinitis near the optic nerve. This case promptly recovered her vision following the opening of the sinus, in which true sinus disease was discovered. So I think we must summarize these cases very much as Dr. Shea has said: many of them are due to other causes than sinus disease. Some of them are definitely due to sinus disease and we must give them the benefit not only of examination of the sinuses and surgery where indicated, but also of thorough general investigation and complete medical treatment to the best of our ability.

Dr. William A. Wagner, New Orleans, La.—My greatest difficulty in deciding whether cases of optic neuritis, retrobulbar or true optic neuritis are due to sinuses or not, depends upon getting the ophthalmologist to cooperate. I send them to the ophthalmologist and receive the usual report made by the usual routine examinations. That does not suffice if one expects to make the proper study of the relationship of the optic nerve to the sinuses, and the effect that the sinuses have on the optic nerve.

When these patients come in with the usual history of impaired vision, and on examination the ophthalmologist finds that he has not the proper accommodation, which is easy to determine in children and young adults, and I will admit probably some difficulty is encountered with the elderly people, it is then that he should check the fields of vision of those patients. He should check the visual fields, particularly the color fields.

When the patient presents other symptoms than those I have already mentioned, paracentral or central scotoma, or contraction of fields of vision for form and color, or definite loss of visual and color acuity and progressive contraction of the fields of vision, I begin to check him rhinologically more thoroughly to see if he presents the usual picture that we see in posterior sinusitis.

The x-ray in the mento-vertex position which we saw on the screen will not delineate the sphenoid unless we put some opaque material into it, and no matter how good the rhinologist is, he cannot do that in the position that I have seen on the screen. I have been trying a long time and I can't do it. I use radiopaque material. Then I go still further. These patients are subjected to many x-rays in various positions. I sometimes duplicate the same position before or after lavage, and I make an oblique (the Rhese) position that was spoken of as being made by Dr. White. It is a good position, but unless the tube is put seven feet away it will not be possible to measure the foramen accurately, and White says that the nerve of any foramen that is larger than five millimeters in diameter is not likely to be subject to a neuritis. On the contrary, if the diameter of a nerve foramen, or optic foramen, is smaller than four millimeters, the nerve is likely to be subjected to damage by infection of the sinuses. Nerves in smaller foramina in my cases were likely to develop neuritis.

I routinely make a Hirtz position, the oblique that I just spoke of, the Rhese, and the Granger, which last, I think, is the best all-round position in so far as its diagnostic accuracy goes, without the use of an opaque oil, but it likewise is false at times, and one cannot always expect to find it accurate.

In some cases I have instilled iodized oil, made pictures in all positions, and found variations in each position in the same patient. I have found also that many sphenoids that are apparently normal on lavage, grossly, in patients whose noses look normal physically, and whose lavage looks clear, are still pathologic. These cases were proven not only by the use of a radiopaque oil demonstrating the thickness of the mucosa, but also by cytologic study of the washings and even by histopathologic study of the mucosa after operation.

I have found another thing to be true in working with the ophthalmologist. Sinuses that are not purulent often cause optic neuritides, and empyemas of the sphenoids often do not. That is worth remembering.

Dr. R. G. Reaves, Knoxville, Tenn.—This disease has been discussed at many of our meetings in the last several years. To me it is quite interesting to hear Dr. Costen say that the neurologists suggest that we operate upon cases with multiple sclerosis. We have been criticized for operating upon too many sphenoids, especially upon those in which we have no proof that disease exists.

Since 1920, I have seen two cases of retrobulbar neuritis due to sinus disease. One was unilateral, a suppurative involvement of the posterior ethmoid and the sphenoid; one was bilateral with pansinusitis; and both of these cases improved after operation. They are the only two cases that I have ever operated upon.

I was with Dr. White when he first started this work and I saw many cases that he opened up that to me looked perfectly normal. For that reason I have never felt that I was justified in opening cases in which I

could not prove the presence of a pathologic condition. I am associated with a man who has a very large eye practice, and I usually examine all of his cases of retrobulbar neuritis. While I am convinced that the condition can come from infection of the sphenoid and ethmoids, like the Mayos, I am convinced that they are quite rare.

I should like to ask Dr. Costen if he has operated upon any cases with multiple sclerosis.

Dr. Costen (closing).—Dr. Alvis described very clearly the rationale which most of us depend upon before we decide to operate. The chances are that I have opened some of these sinuses needlessly, but at the moment we were all agreed that that should be done, and so, figuring that the risk of permanent injury of the eye was worth that surgical risk, the surgery was done.

I was interested to hear Dr. Wagner emphasize the elaborate x-ray study. I presented these x-ray specimens mainly to show the wide variation in the sphenoid; as a matter of fact, I do not depend so much on the x-ray to make up my mind as I do on the combination of the appearance of the local condition in the nose about the posterior sinuses, the opinion of the ophthalmologist as to the rapidity and gravity of the lesion, and the presence of headache.

I note in the paper (which you will see in the record) those who complain of chronic headache, and I assume from that, if they have the typical sphenoid headache, that it is a deciding factor in whether I am dealing with a pathologic sphenoid or not.

Dr. Reaves asked if I had opened any cases of multiple sclerosis; the one which Dr. Alvis mentioned, which he finally decided was a multiple sclerosis, is the only one I know of. None of those presented in this series was recorded, so far, as showing multiple sclerosis.

SURGERY OF THE BILIARY TRACT*

By ARNOLD S. JACKSON, M.D.
Madison, Wisconsin

A case recently observed will serve to illustrate the first point I wish to make in this discussion of the surgical treatment of biliary tract disease. The patient, a male, aged 45, was taken suddenly ill while doing some painting in his home. He complained of a dull, localized substernal pain that was accompanied by nausea. His physician diagnosed the trouble as an acute attack of cholecystitis that had followed two days of dietary indiscretion. The diagnosis was based on the presence of a tender mass in the region of the gallbladder. A quarter grain of morphine was given hypodermically and local heat applied. As the symptoms persisted, I was called in consultation some hours later and on examination found splinting of the entire right rectus muscle with tenderness most marked in the right upper abdomen. That the patient was suffering from an attack of acute cholecystitis appeared probable, although, the possibility of a high-lying retrocecal appendix could not be absolutely eliminated.

He was removed to the hospital, where the leukocyte count was found to be 14,400, with a polymorphonuclear count of 75 per cent. The temperature and respiration were normal. While the patient experienced no attacks of colic, he was in evident distress from distention. He was given an enema, intravenous glucose as the urine showed a trace of acetone, and duodenal suction was started. The following day the leukocyte count was 18,200, the temperature 99.2°; otherwise, his condition was about the same.

The probability of a mass in the region of the gallbladder seemed more evident, but at the same time tenderness was present at McBurney's point. A flat abdominal x-ray plate was negative as far as revealing the presence of a gallstone shadow.

The question now arose as to whether we should consider this patient as having an acute surgical abdomen and perform an immediate laparotomy or whether conservative treatment should be continued. The most probable diagnosis was that of acute cholecystitis, the mass together with the absence of chill and high fever suggesting hydrops of the gallbladder. If surgery was delayed, the possibility of a perforation occurring had to be considered; also, gangrene and empyema might develop. There was a slight chance that perforation and a localized abscess of a retrocecal appendix might have occurred as indicated by the rising leukocyte count.

It has been the policy of the Jackson Clinic to deal conservatively with cases of acute cholecystitis unless a rising leukocyte count, and increasing toxemia as indicated by a chill and elevation of the temperature, suggest a beginning gangrene or empyema. We often do not see these patients until several days after the onset of an attack, at which time, they may show evi-

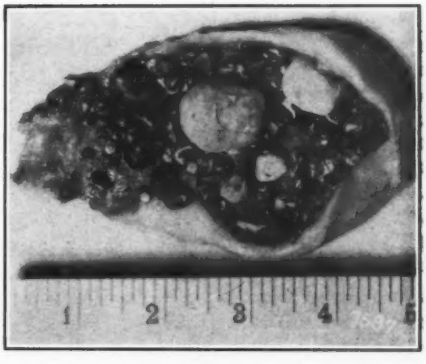

Fig. 1
Case of acute cholecystitis with gallstones described in the text.

*Read in Section on Surgery, Southern Medical Association, Thirty-Third Annual Meeting, Memphis, Tennessee, November 21-24, 1939.

*From the Jackson Clinic.

dence of acidosis, dehydration and an acutely tender abdomen. After one to several days' therapy, the acute symptoms usually subside, the blood count drops, the fever and toxemia diminish, and the patient is in far better condition to withstand surgery. In an occasional instance the reverse of this picture is true and further to delay operation is only to invite disaster.

In spite of the fact that this policy is no longer advocated by some leading surgeons, we have persisted in using the method that has yielded satisfactory results in our experience. Surgeons advocating immediate operation in acute cholecystitis claim certain advantages, namely, that the anatomy of the ducts is not distorted by inflammatory changes and there is consequently less possibility of injuring the common duct. This assertion cannot be disputed, but whether this advantage outweighs the risk of operation at the peak of a toxic condition is still a matter of argument.

As regards the case under discussion, after three days all acute symptoms subsided, leaving a well-defined mass in the region of the gallbladder. Operation revealed hydrops of the gallbladder that was removed without difficulty and the patient went on to an uneventful convalescence.

The relative merit of cholecystectomy vs. cholecystotomy was for years a common topic at medical meetings. The question is seldom debated today, as it is generally agreed that a diseased gallbladder should be removed unless the risk of cholecystectomy is too great. It has been our policy to reserve cholecystostomy for certain acute cases where emergency operation seemed imperative yet the risk of removal prohibitive. In the elderly, the debilitated and in patients who have been jaundiced for long periods, such indications occasionally arise. The pendulum having swung too far in favor of always removing the gallbladder, we believe that most surgeons are now taking a more conservative stand. Moreover, it was ascertained by Harry Mock, among others, that a follow-up cholecystogram study made of a group of 40 patients who had undergone cholecystostomy 6 months to 20 years previously, showed normal gallbladder visualization in 68 per cent of the cases. I am not advocating cholecystostomy, but I do not believe that the gallbladder should always be removed.

Even among our staff there has existed a difference of opinion regarding the question of drainage following cholecystectomy. My late brother, Reginald, and I have always preferred the use of a small, soft rubber tube after removal of the gallbladder. Two ligatures of the cystic duct are made, the second being left long, and over this is threaded the tube so that it rests securely in place at the logical point in case of bile leakage. This tube is shortened for three days and usually removed on the eighth postoperative day.

At about the time that I stopped using drainage for thyroidectomy, my brother, James, discontinued using drains following cholecystectomy. In one or two instances he has had to reopen the abdomen for bile leakage, but on the whole, his cases have done exceptionally well. They are out of bed 2 or 3 days earlier and likewise are discharged from the hospital sooner. Presumably they should have fewer postoperative adhesions and consequently less chance of subsequent complications. The wound should be stronger and there should be fewer instances of postoperative hernia. In analyzing a series of 800 cholecystectomies performed by our staff, I found a lower mortality rate in the non-drainage group of cases. Further study, however, served to confirm the old adage that if one tries hard enough statistics can be made to tell anything, even the truth. What the first analysis did not show was the fact that all the bad risk cases, including gangrene, empyema and perforation were drained and that naturally added to the mortality rate in this group.

Although my results have been markedly improved in so far as decreased drainage and improvement in the scar are concerned following thyroidectomy, the same problem does not exist in gallbladder surgery. Regardless of how much care is exercised, in an occasional case, some leakage of bile may occur. The late great Willy Meyer confided to me that this had been his experience after performing a series of nearly 500 cholecystectomies without drainage, and that he had consequently resumed draining his cases. The advantages of non-drainage do not seem to me to outweigh the risk of occasionally jeopardizing the patient's life through the media of bile leakage and peritonitis when a drain is not used.

Frank Lahey advises exploration of the common duct in a high percentage of his cases, while some surgeons favor a more conservative stand. Although I have the greatest respect for the judgment and ability of perhaps America's number one surgeon, I feel that it may not be a good policy for the average surgeon to explore the common duct in a high percentage of cases. The

danger of injury to this vital structure, together with the subsequent complications that occasionally occur regardless of who performs choledochotomy, calls for conservatism on the part of most surgeons. Dr. Lahey has pointed out, and rightly so, that many stones in the common duct cannot be palpated and unless the duct is opened they will be overlooked. Such an experience occurred to me recently when, after a negative palpation of the duct, I opened it and removed 40 small stones. However, the duct was definitely enlarged and thickened and the sclera showed icterus. Lahey has shown by his own figures that in the past when he failed to open the common duct he not infrequently missed stones. Still, we have explored the duct only when certain definite indications have existed, such as: a history of jaundice, a palpable stone, a small contracted gallbladder full of stones, hydrops of the gallbladder or an enlarged common duct.

As regards drainage of the common duct, we have used the T-tube since it was first called to our attention several years ago by Starr Judd. The length of time that it is left *in situ* depends entirely upon the individual case and may vary from 2 weeks to several months, but in most instances 3 or 4 weeks will suffice.

Since the routine adoption of spinal anesthesia for abdominal surgery in our clinic in 1928, there has been a marked decrease in postoperative complications. In a recent study of 800 operations on the biliary tract the mortality rate was found to be 4.8 per cent, but for those cases operated upon under spinal anesthesia only 3.2 per cent. This series included all types of cases, such as perforation with peritonitis, obstructive jaundice and malignancy, etc. Not only is the operation greatly facilitated and simplified by spinal anesthesia, but postoperative complications such as pneumonia, embolism and phlebitis are largely eliminated. It is, of course, impossible to get away from the age factor in mortality and 17 of the 37 deaths in this series occurred in persons over 60 years of age.

The most recent contribution to biliary surgery has come from the field of medicine and has already proven a valuable aid in lowering mortality in obstructive jaundice. Vitamin K has been used successfully in a series of ten jaundice cases at our clinic in recent months and in every instance it has prevented hemorrhage either during or after operation. This valuable aid may be further augmented by a recent discovery from the field of chemistry, a coagulant containing oxalic acid, discovered by Steinberg and obtained from the common weed, shepherd's-purse. This gives promise of a simple effective method of preventing or checking hemorrhage.

Chart 1

1,237 CASES OBSERVED AT THE JACKSON CLINIC

903	Cases operated upon for gallbladder disease
800	Cases used in this study
632	Number of females
168	Number of males

Chart 2

PATHOLOGICAL ANALYSIS

598	Cases of chronic cholecystitis
568	Contained gallstones
102	Acute cholecystitis
38	Cases of gangrene
30	Strawberry type
28	Cases of acute empyema
21	Perforation
13	Malignancy

Chart 3

ANALYSIS OF 800 CASES OF GALLBLADDER DISEASE

568	Gallbladder contained stones
488	Complained of upper abdominal distress
385	Complained of nausea or vomiting
190	Had indefinite complaints
183	Had gallstone colic
137	Mentioned jaundice

Chart 4

ANALYSIS OF 800 OPERATIONS FOR GALLBLADDER DISEASE

397	Had cholecystectomy only
283	Had cholecystectomy and appendectomy
137	Had operation for disease of the biliary tract, plus other abdominal surgery not including appendectomy

Chart 5

OPERATIVE MORTALITY ANALYSIS

Number of gallbladder operations	800
Number of deaths	37
Mortality percentage	4.8
Deaths include:	
8	Cases perforation with peritonitis
5	With obstructive jaundice
15	With multiple operations
4	With pulmonary embolism
3	With hypertension
2	With intestinal obstruction
20	Were over 50 years
17	Were past 60 years

Chart 6

END RESULTS OF OPERATION OF THE BILIARY TRACT DETERMINED BY QUESTIONNAIRE

Records studied	800
Died following operation	37
Died from other causes subsequently	17
Letters returned unclaimed	251
Answered questionnaire	457
Number cured	319, or 69.8 per cent
Number improved	119, or 26 per cent
Number noted change	19, or 4.1 per cent
Free from colic	352
Free from gas and belching	309
Free from pain	263
Attacks of colic	85
Attacks of gas and belching	113
Attacks of jaundice	58
Attacks of pain	154

In the postoperative care we use duodenal suction in nearly all cases and feel it is important in preventing such complications as gastric dilatation, distention, ileus and obstruction. Patients are permitted to lie on their backs for short periods only during the first 48 hours to prevent atelectasis and pneumonia, and they are encouraged to chew gum to prevent parotitis. We believe that failure to turn the patient frequently in the early stages and permitting him to remain too long in bed causes venous stasis, phlebitis and embolism. All patients are given deep breathing exercises and passive movements after the third day, they dangle on the tenth and are out of bed on the twelfth day, unless obesity or the wound are contraindications. The few cases of phlebitis that have occurred have been successfully treated by leeches as suggested by Oschner.

In conclusion, I should like to point out a few facts regarding the disappointing results occasionally seen following operations on the biliary tract. Recently I reviewed a series of 1,237 patients with gallbladder disease observed at the Jackson Clinic between the years 1922-38. In this series 903 patients were operated upon and 800 cases were traced and checked for this study. Only 69.8 per cent of this group admitted that they were cured. Nearly one out of four claimed they were not cured, but admitted an improvement as a result of operation and 4.1 per cent said there was no change in their condition.

Unsatisfactory as these figures may appear, they are fairly representative of those generally obtained, and the reason is largely due to too long delayed surgery. If the operation is performed early before secondary changes have occurred in the liver and other organs, the results are far more satisfactory. It was shown by Graham as well as by McCarty and myself that hepatitis and cholecystitis are commonly associated, and that the degree of liver involvement is directly proportional to that of the gallbladder. Consequently at operation the extent of recovery can be well prognosticated by the amount of hepatitis and pancreatitis present. The deduction to be drawn from disappointing results of gallbladder surgery is to make clear to patients the unfortunate consequences of delayed operation. The surgeon cannot be blamed if the patient continues to suffer from flatulence and indigestion when the liver has been found to be badly diseased.

PERIRECTAL ABSCESS*

By WALTER A. FANSLER, M.D., F.A.C.S.†
Minneapolis, Minnesota

Abscesses which present themselves in the region of the anus and rectum usually originate from one of five causes:

(1) Infection in adjacent organs and structures.

(2) Injuries and infections of the crypts of Morgagni.

(3) Injury and infection of the perianal skin and tissues.

(4) Hypodermic injection of medicants.

(5) Injury and infection of the wall of the rectum with perforation.

(6) Injury and infection of the rectal wall without perforation.

The location of an abscess in relationship to the anus, rectum, and other perineal structures, depends in most instances upon the site of origin of the primary infection. This is true because its initial spread is limited by definite anatomical structures. In neglected and complicated cases, anatomical barriers may be broken down, but in the beginning there is usually but one anatomical space or compartment involved. Considered surgically, there are six of these compartments about the rectum. The most external of these spaces are the ischiorectal fossae,

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†Clinical Associate Professor of Surgery, University of Minnesota Medical School.

which are present on either side of the lowermost portion of the rectum and anal canal. These are pyramidal-shaped with the base directed outward and covered by the skin between the anus and ischial tuberosities. Mesially the boundary is the lowermost part of the rectum and anal canal, and laterally the ischial tuberosities. Posteriorly they are bounded by the gluteal muscles and anteriorly by the levator muscles. The superior boundaries of the roof are also the levator ani muscles and fascia. These two fossae have no connection except posteriorly, where there is a narrow communication, just underneath the anococcygeal ligament. It is through this narrow channel that infection may extend from one fossa to the other, thus forming a so-called horseshoe abscess.

Above the ischiorectal fossae and separated from them by the levator ani muscles and fascia, are the supralevator spaces. Laterally these spaces are bounded by the obturator internus muscle and fascia, mesially by the rectal wall, above by the pelvic peritoneum, and below by the levator muscles and fascia. The levator muscles and fascia thus form the roof of the ischiorectal fossa, and the floor of the supralevator spaces. The fifth compartment lies posteriorly to the rectum, the retrorectal space. Laterally the space is bounded by the two layers of fascia, which converge to the rectum from the obturator internus fascia, the so-called rectal stalks. The anterior boundary is the rectum, the posterior boundary is the anterior surface of the sacrum and coccyx. The sixth space is the one which lies between the mucous and muscular coats of the rectum, the intramural space. This space has no communication with the perirectal spaces; hence pus occurring here lies wholly within the rectum. While the diagnosis of an abscess in this region is usually quite simple, in some instances most careful consideration must be given before one comes to a decision. A typical abscess forms rather quickly and is indicated by pain and the formation of a tender indurated mass. Other conditions which result in a mass in this region are usually slow-forming, relatively painless, and do not show evidence of inflammation. Among these latter conditions may be mentioned: adenoma, lipoma, myona, sarcoma, endometrioma, dermoid, meningocele, oleoma and gumma. The difficulty in differentiating comes from the fact that some abscesses form slowly with little pain or tenderness, while occasionally some of the other conditions form rather rapidly and are accompanied by pain and secondary inflammation. This is particularly true of a rapidly growing sarcoma.

One of the most helpful maneuvers in determining the character and extent of a lesion is the so-called bidigital examination. The index finger is inserted into the rectum and all adjacent tissues are carefully palpated between the tip of the finger and thumb. Lesions other than abscesses are likely to give a more definite and distinct outline than that of an abscess. In the female a pelvic examination is often of great assistance in differential diagnosis, and in determining the extent of the condition. Blood studies may also be of help. In rare instances a biopsy may be necessary before a definite decision can be made.

Having decided that the condition is an abscess, the number of spaces involved and the site of the primary infection are the most important considerations. The most frequent site of the primary infection is in the rectal wall, but the female organs, the prostate, the seminal vesicles, the posterior urethra, sigmoid diverticula, high rectal strictures, appendical abscess, Pott's disease, and various pelvic infections may be the source of the abscess. In these instances the general condition of the patient, and the fact that symptoms are not limited to the perineal region, usually suggest that more extensive disease is present. The ultimate disposal of these cases is not within the scope of this paper, but preliminary drainage through the perineal region or rectum is usually indicated. It should be recognized, however, that this is but an emergency measure, and more extensive subsequent procedures will be necessary to cure the patient.

The most frequently noted abscess occurring about the anorectal region is one involving the ischiorectal fossa. In almost every instance a simple ischiorectal abscess originates from infection in a crypt of Margagni, the sequence being infection of the crypt, spread through the bowel wall, and infection of the fat in the ischiorectal fossa with abscess formation. This is usually indicated by pain accompanied by the rapid formation of a tender, red and indurated mass. This, however, is not always true, and it is the atypical cases which may lead to confusion in diagnosis. In some instances of infection by an organism of low virulence, a small non-painful, slightly tender mass appears which increases in size over a period of two or three weeks. Finally the skin over the area may become somewhat

reddened and eventually it ruptures. In other cases where there is a fairly large primary opening, drainage may occur back into the rectum. In this case the indurated area recedes in size without draining externally, or even with external evidence of abscess. The internal opening of an abscess of this type is usually quite large and is easily found by careful probing of the crypts of Morgagni. A slow forming nonpainful abscess is also characteristic of an uncontaminated tuberculous abscess, but when it ruptures or is incised, the discharge is a thin watery flocculent material, rather than the typical pus of ordinary pyogenic organisms. Occasionally, crepitation may be felt over the affected area. It is most important to determine whether the gas is within a cavity, or whether it is diffused through the tissues. If the gas is within a cavity, it usually indicates one of two things: first, that there is a sizable opening between the abscess cavity and the intestinal tract, or secondly, that the infection is due to a gas-forming organism. Diffusion of gas through the tissues usually indicates the presence of gas gangrene and is accompanied by prostration and other evidence of severe illness. It is essential that serum be given quickly, and even with early serum treatment, the prognosis is extremely serious. In rare instances the infection may be due to a virulent streptococcus. This produces a rapidly spreading fulminating type of abscess. Often not more than twenty-four hours may intervene from the onset of symptoms until the formation of a well developed abscess. I have seen two fatal cases of streptococcus septicemia originating in a perirectal abscess.

There is some difference of opinion as to the proper time to operate upon an ischiorectal abscess, but I believe early operation to be advisable. Delay only prolongs the pain incident to pus under tension and invites spread of the infection. We have never seen any ill effects from early drainage, even though the abscess is deeply seated, and it is necessary to incise through normal skin and several centimeters of healthy fat before the abscess cavity is encountered. Treating these abscesses expectantly with the idea of allowing them to "point" on the surface, invites a greater destruction of the fat in the ischiorectal fossa, and the formation of a larger abscess. It also encourages the spread of the abscess posteriorly to the opposite fossa, forming a horseshoe abscess about the rectum. An early release of the tension stops the further destruction of tissues and starts the patient upon the road to recovery. Since in the majority of instances there is an opening into the rectum, the moment the abscess cavity ruptures or is drained externally, we are actually dealing with a rectal fistula. This being true, we must decide whether or not to deal with the fistula immediately, or simply drain the abscess and leave the fistula to be dealt with at a later date. If an internal or primary opening is present, it is usually in a crypt of Morgagni, and it can usually be discovered by gently searching the crypts with a fine probe bent into a hook. If the opening cannot be demonstrated in this manner and the abscess is incised, the probe can then sometimes be passed through from without. The cavity should be searched gently and not roughly, for in inflammed and friable tissues it is easy to create an opening where one did not exist. If the probe cannot be passed without force, the attempt should be abandoned.

Where the abscess is relatively small, and the internal opening can be demonstrated, we believe that the probe should be passed into the rectum and the overlying tissues divided, thus completing the operation for both the abscess and fistula at once. Where the abscess cavity is larger, or the internal opening cannot be demonstrated, we usually resort to drainage only. In the case of large abscesses, incision through the sphincters results in wide separation of the severed ends of muscle with subsequent gutter formation and deformity, and greater impairment of sphincter function. If, because of the size of the lesion or the fact that no internal opening is found, incision only is decided upon, we have found it advantageous to do it in a certain manner. The incision should be ample and made as a cross or T incision. One arm of the incision should be carried toward the anus until the fibers of the external sphincter muscle are well exposed at a point nearest the internal opening or the crypt where the opening is thought most likely to be. It will then be but a short distance from the end of the incision to the internal opening, and the subsequent incision for curing the fistula, if one is present, will be short. In fact, the length of the fistulous tract is but the width of the sphincter muscle. We also find it often advantageous to remove a portion of the skin overlying the abscess,

a procedure we have referred to in a previous paper as scalping. This allows drainage and contracture of the wound without subsequent packing.

External injuries or infection in the perianal skin may produce the formation of furuncles, or abscesses which simulate an ischiorectal abscess. Bidigital examination will usually enable one to outline the affected area as distinctly separate from the rectum and anal canal. This is demonstrated by the fact that the examiner can palpate an area of normal unindurated tissue between the rectum and area of induration. Simple incision of these lesions is all that is needed to relieve them.

Sterile or non-sterile abscesses in this region are also sometimes seen following the injection of various medicants. They have become more frequent since the widespread use of various types of injections for hemorrhoids, prolapse, pruritis ani, fissure and postoperative pain. They usually result from unsterile technic, or the "pooling" of the medicant, particularly those in an oily base. Simple drainage is sufficient to relieve the condition, and the sooner it is done the better.

Injuries and infections in the wall of the rectum above the cryptic area with perforation usually produce abscesses in the supralevator or retrorectal spaces. Perforation of the wall by foreign bodies, the too deep injection of medicants, and severe ulceration, are commonest causes. Symptoms are deep, aching pain well up in the rectum, and usually some constitutional symptoms. These are the cases which are most frequently not diagnosed in the early stages, the patient having been dismissed with a suppository. If neglected, the infection will, in most instances, spread to the ischiorectal fossa and present itself externally. This usually means an operation for a fistula whose internal opening is high above both sphincter muscles with subsequent faulty control of the bowel content. The diagnosis is made by digital examination, a tender mass being felt in the region of the supralevator or retrorectal space, the ischiorectal fossa being normal and indurated. These abscesses should be drained internally by liberal incision through the wall of the rectum. Care should be taken that the lowermost part of the incision corresponds with the lowermost portion of the abscess cavity. If the point where the levator ani muscles and fascia join the rectum is kept in mind, the location, size and extent of the incision necessary are easily determined. If the abscess is in the retrorectal space, the incision should again be ample and low on the posterior rectal wall. These incisions should be kept open by daily digital examination until healing is complete.

Infections and injuries to the bowel wall without perforation often result in the so-called intramural abscess. In this case the pus is situated between the mucous and muscular coats of the bowel. There is no external evidence of the abscess. Internal pain, aching and constant in character, with or without constitutional symptoms, occurs. Digital examination reveals a tender, often fluctuating mass. It is usually quite evident on palpation that the mass is within the rectum and does not extend beyond the muscular coat. If this type of abscess is not incised, spontaneous rupture into the rectum usually occurs. The patient has a sudden relief from pain, and a gradual subsidence of the soreness. The pus may be evacuated with the stool and is often unnoticed by the patient. The abscess will often recur or a submucous sinus remain. As soon as the abscess is discovered it should be incised from end to end. After treatment consists in rectal irrigations and keeping the margins of the wound apart digitally until healing has occurred.

There is such a variation in the character of the abscesses involving this region that general conclusions cannot be drawn. Three things, though, are important in all instances. First, the extent and source of the lesion should be definitely determined before surgery is attempted. Second, consideration of the anatomical relationship of the region is important if the condition is to be cared for in the best manner possible. Third, in every instance drainage, either as a preliminary or curative means, should be established at the earliest possible moment.

DISCUSSION (*Abstract*)

Dr. Jno. L. Jelks, Memphis, Tenn.—The most youthful case of perirectal abscess and complete fistula that I have operated upon occurred in a baby 5 months old. We who operate upon many such abscesses know that

there must usually be an internal opening, that this internal opening is in most cases to be found in a crypt, that this internal opening must be excised as are also the fibrosed walls of old abscesses and fistulae, thus leaving a clean surgical wound; that even though there are found multiple internal openings they each will probably be in a crypt and each must be dealt with in the same manner. Sometimes the internal opening may be found high, as in those cases in which pressure necrosis has caused high rupture. Some such cases may require the seton or ligature operation. I believe that at least 25 per cent of the perirectal abscesses referred to me have resulted from the injection treatment.

These abscesses should never be "just opened" like abscesses elsewhere, but as described by me about 1900 in the Asheville meeting of the Mississippi Valley Medical Association, the abscess must be so widely opened that its cavity will represent the apex of a triangle.

It is my practice to operate upon all these cases as early as I can have them hospitalized and prepared. Why wait for greater and more extensive destruction of tissue or for an ischiorectal abscess to break into the superior pelvirectal space or beneath the rectococcygeus to involve both ischiorectal spaces, so they are treated as emergencies always. It is my practice also always to excise any existing hemorrhoids and thrombosed perianal veins. The hemorrhoids will enlarge and drop into the wounds like a ball-in-socket joint, encourage contractions and retractions of the sphincter, retard or prevent healing and leave more wound deformity. Deformities are not seen, but should be regretted.

It is my custom to hold the ends of the severed muscle in near but not complete approximation for four to seven days to insure sphincteric control, less scarring and more rapid healing of the wounds.

It is with pride that after thus operating upon these cases, trimming edges and excising related pathologic tissue, I note their complete healing with less deformities and I dismiss them as happy and satisfied patients.

Dr. Emmett H. Terrell, Richmond, Va.—I agree thoroughly with Dr. Fansler that perianal and perirectal abscesses must be incised in every instance as soon as the presence of pus is proven. A definite diagnosis is not always easy, however. When some uncertainty exists, as not infrequently happens, palliative measures should be employed and incision deferred until no further doubt exists. Embarrassment may be avoided sometimes by inserting into the suspected abscess a needle of fairly large caliber attached to a tight-fitting syringe. If pus is obtained by withdrawal of the plunger then incision in line with the needle can be safely made.

In this connection it is most important that a circumscribed collection of pus be differentiated from a spreading cellulitis. In the latter condition an incision generally is not indicated, but may aggravate and cause a spreading of the infection. A cellulitis in the region of the rectum should always be looked upon with concern, and it is important that it be recognized early. In its incipiency it responds readily, in most instances, to x-ray judiciously given.

I do not agree with Dr. Fansler that deep abscesses, such as retrorectal and superior perirectal may be safely opened through the rectal mucosa. I believe with Dr. Jelks that it is best to drain them by wide incisions through the perianal skin.

Dr. Fansler (closing).—I agree with Dr. Terrell in stressing the necessity of two-stage operations in many cases in which a fistula exists, and in most cases a fistula does exist.

It is our custom in all cases to endeavor to determine whether an internal primary opening is present. This is done by searching the crypts and other suspicious internal areas with a bent probe. If this is unsuccessful, a probe is inserted into the cavity externally, care being taken not to make an opening where none exists. If an opening is discovered and the abscess cavity is small, we then divide through the fistulous tract immediately, completing all necessary surgery at one sitting.

On the other hand, if the abscess cavity is large, we feel it is better simply to drain the abscess, allow the cavity to shrink down, and then at a later date operate upon the fistulous tract. If the sphincter is divided in the presence of a large cavity, the severed ends of the muscle will retract more widely. There will be greater deformity, and perhaps not as good control, than if the cavity is allowed to contract before the muscle is divided.

While I believe in early operation for these abscesses, I also quite agree with Dr. Terrell that we must be sure we are dealing with an abscess. In rare instances this is difficult, and I once had the experience of incising what appeared to be an abscess, but on section was found to be an extremely rapidly growing lymphosarcoma.

I have also had the experience of losing a patient through metastatic infection originating in the perirectal region. This is a rarity, but it is a consideration which cannot be dismissed entirely in dealing with this condition.

The only point upon which there seems to be any difference of opinion is the question of the drainage of the supra-levator abscess. In these cases the discussants all drain the abscesses externally, which is the time-honored orthodox method. None, I believe, has tried the method of internal drainage which I have found satisfactory and believe to possess many advantages over external drainage.

In internal drainage the incision must be very liberal and extend to the lower-most point of the abscess cavity; namely, the lower insertion of the levator ani muscle, which is usually along the upper portion of the anal canal. If the shape and anatomical relationship of the supra-levator spaces are kept in mind, this incision can be large and still be done with safety. In this case the cavity will collapse down and heal in satisfactorily without the creation of an extensive fistulous tract, which later necessitates the division not only of both sphincter muscles, but often the portion of the bowel wall.

THE MANAGEMENT OF PROLONGED LABOR*

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The generally accepted average duration of labor is eighteen hours for primigravidae and twelve hours for multigravidae. Obviously, to establish this average there must be many cases of labor which occupy considerable more than the average time. Not all such cases are necessarily pathologic. Nor is it possible to state in terms of time alone when a labor is pathologic. The best definition would be a relative one. A labor may be said to be pathologically prolonged when advancement toward its termination ceases to be commensurate with the amount of force estimated to be exerted on the fetus by the contractions of the uterus.

It is thus very evident that the total elapsed time between the beginning of labor and its termination may not in all cases be identical with the actual time of labor. Intervals of cessation of effective pains occurring either spontaneously or as the result of opiates or other drugs must be subtracted from the total elapsed time, much in the same way that "time out" in a football game must be subtracted from the total elapsed time which the game takes to arrive at the time actually consumed in play. Understanding of this viewpoint is particularly necessary to impress on the patient and her friends in order to meet the psychological problem which their natural anxiety often presents to the obstetrician.

But, recognizing all these factors of uncertainty as to exactly when any labor should be regarded as unnaturally prolonged, it does become necessary for purposes of discussion to adopt an arbitrary time limit beyond which labor may be so regarded. For our present purpose we have chosen thirty-six hours as that limit. We have reviewed 500 consecutive cases so defined which have occurred in a series of 8,446 cases in our clinic during a period of one and a half years.

First of all, even though they be considered pathologic, not all of them are insusceptible of spontaneous delivery. We find that more than one-third of them will deliver spontaneously. In general, there tends to be a progressive decrease in the proportion of spontaneous deliveries with increased duration of labor. It will be noted that there is considerable irregularity in the incidence of spontaneous delivery in the cases above sixty hours. This is probably accounted for by their relatively small numbers. Even up to the eighty hour limit, however, spontaneous delivery occurs in somewhat over one-third of the cases.

We find then that about six out of ten of these cases cannot be expected to deliver themselves spontaneously and that some artificial factor of management will have to be depended upon to secure their outcome.

The estimation of the factors of dystocia involved, and the choice of particular forms of artificial interference, constitute the problem presented to the obstetrician, and its solution determines the competence of his work.

The factors entering into the necessity for interference are numerous. They involve the forces concerned in labor, the size and condition of the passage through which the fetus must be forced, and the size, presentation, position, and other characteristics of the fetus itself. In relatively few cases may any one of these several factors be considered by itself. Nearly always one depends in varying degree upon the others. More often than not one is faced with a rather complex problem in endeavoring to evaluate any given situation.

Many factors may be considered in determining the efficiency of the uterine contractile power. The woman's general physique, her robustness of health, the innervation of the uterus, its anatomical development, hormonal influences, the psychic state of the patient and, in modern practice, the influence of analgesic drugs may all affect the efficiency of uterine muscular action. There is no doubt that inadequacy of uterine power plays an important role in the undue prolongation of many labors. In some it may be assessed as the sole cause of such prolongation. But very frequently it coexists with some degree of proportional inadequacy of the pelvis. It is not improbable that there may be a common endocrinal basis for inadequacies both of the pelvis and of the uterine forces.

Unfortunately, we have no present satisfactory method of measuring the power developed by the labor contractions of the uterus. Fen-

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ning, Davis and Adair,* in a recent communication, have offered a method of "indirect external hysterography." They use a specially designed electrode with sensitive string galvanometer by means of which kymographic tracings of uterine activity are obtained, the amplitude of the excursions on the graph having a definite relation to the force of the uterine contractions. They say in their summary, however,

"Potentially the method has considerable promise. * * * The apparatus at present is not electrically or mechanically perfect."

Murphy and his co-workers have recently exhibited results obtained by the tokograph, of which several models have been from time to time in the past presented. This method also would appear to have promise, but as yet I have had no personal experience with it. Methods depending upon the introduction of electrodes or aerostatic balloons or hydrostatic bags into the uterine cavity during labor are obviously not susceptible of general clinical use.

We are therefore thrown back upon the very fallacious observation of physicians and nurses of the behavior of the woman in labor. Such observation includes the frequency and duration of contractions, the firmness of the uterus during pains and the notoriously variable subjective reaction of patients to such contractions. This method is obviously entirely lacking in quantitative accuracy. When conducted by several individuals, as it must be when labor extends over very protracted periods, its value is small. Moreover, estimation of the adequacy of uterine contractions in terms of work performed is nearly hopeless. This is especially true during the first stage of labor, inasmuch as at this time the whole force of the uterus may be expended in molding the presenting part. The progress of this molding is most difficult to estimate by the observation of changes, except over long intervals of time.

In considering the size and configuration of the pelvis, note that we must deal with the whole pelvis. This distinction is most important because nearly all the methods of pelvic mensuration, either by physical examination or x-ray, are concerned directly with the bony structure of the pelvis. All information referable to the bony structure is of the utmost importance, but it by no means constitutes a wholly satisfactory basis for estimating the actual capacity of the pelvis itself. This fact is responsible for many of the dilemmas in which we find ourselves, in which actual labor experience fails to justify good prognosis based on competent study of the bony pelvis. It also serves to accentuate the important fact that competent physical estimation of the pelvis by the resources inherent in our brains and fingers is in the last analysis more important than are x-ray findings.

Although x-ray examination of the pelvis is an important contribution to our total knowledge of the conditions in any case, it must be regarded as are all other laboratory adjuncts to physical examination. It supplements but does not replace the physical findings. Dependence on it alone invites disaster. Such dependence should be proportional to the care and elaborateness of the technic used in the x-ray examination. Unless carried out by technics especially designed for this purpose, x-ray examination of the pelvis as an aid to estimating its obstetric competence is a sheer waste of film.

But no matter how competently made, estimation of the pelvis itself is of significance only in relation to the other two great factors concerned in the normal evolution of labor. It must be related to the fetus, and both in turn to the competency of the labor forces.

The methods of fetometry at present available are unsatisfactory. The general size of the fetus may be estimated by external examination of the patient's abdomen, but there inhere in this method rather wide limits of error. I am not convinced of the special accuracy or value of any method of x-ray fetometry yet proposed.

The polarity of the fetus and the position of the presenting part may, of course, be determined with considerable accuracy by ordinary means of physical examination supplemented under some circumstances by roentgenography.

But the size, presentation and position of the fetus do not tell the whole story concerning the probability of a particular fetus' being born naturally. Some of the intangible factors constituting a part of every obstetric problem pertain to the fetus itself. Among the most important of these intangibles are the moldability of the head, the general stamina of the baby as determined by its inheritance, by the state of the mother's health during pregnancy, and by correct nutritional factors involved in the mother's dietary. Then there are such specific factors as the fragility of the fetal blood vessels, their per-

*Fenning, Con.; Davis, M. Edward; and Adair, Fred L.: Amer. Jour. Obst. & Gyn., 38:670 (Oct.) 1939.

meability, and the state of the fetal blood. It is obvious that none of these details can be estimated in advance of labor. Yet some of them may be most important in influencing the outcome of labor and any may determine the survival of the fetus.

In consideration of the several obstructions to the easy passage of the fetus which the expulsive forces of labor must overcome, attention is frequently concentrated upon the cervix and the pelvic floor. In regard to the cervix, one frequently hears the phrase "cervical dystocia" or its equivalent, assigned as a cause for the prolongation or obstruction of labor. Many operative procedures have been devised to overcome the alleged rigidity or undilatability of the cervix. Heretical as it may sound to some of you, I am firmly convinced that the cervix, except when grossly diseased, as by new growth or extensive cicatrization, is almost never *per se* the cause of arrested labor. Time will not permit a thorough discussion of this most important statement. But frequently I have been able to demonstrate to myself and my co-workers the ease and rapidity with which the cervix, apparently constituting obstruction, dilates when other coexisting factors of dystocia are overcome. So I more and more firmly believe that "cervical dystocia" is one of the least frequent and least important of all the factors concerned in the obstruction of labor. This fact is attested by the relatively great rarity with which it is found necessary in our clinic to resort to such procedures as trachelotomy, Dührssen's incisions, or manual dilatation of the cervix in the management of delayed or obstructed labor. It is to be remembered that this represents experience shared by several qualified chiefs with entire individual autonomy of clinical judgment and practice. Personally, I believe that such procedures as I have alluded to hold only the rarest legitimacy in our management of these cases.

The same consideration does not apply to rigidity of the pelvic floor, although it is perfectly obvious that even this factor in many cases attains importance only in relation to the dimensional and conformational characteristics of the pelvic inlet and outlet. And as the means for overcoming rigidity of the pelvic floor are relatively simple, argument about it is unimportant.

In all that has been said of the difficulties of estimation of the numerous factors involved in the prolongation of labor in definitely quantitative terms, I would not have you suppose that the obstetrician is helpless in attempting it. On the basis of careful physical examination, augmented by some of the other methods indicated, and fortified by adequate experience, the competent obstetrician is capable of attaining a high degree of prescience in regard to these matters. But there his capacity ends. In only a small proportion of cases is he legitimately able to say in advance of some trial of labor that a particular woman well within the favorable childbearing age limit and with a uterus uninjured by prior trauma will definitely not be able to deliver in the normal fashion and must inevitably be subjected to elective cesarean section. Nearly all our cases which are finally terminated by any form of artificial interference are subjected to observation of behavior during labor. We believe that only so may decision as to termination of labor by artificial means be legitimately arrived at.

In relation to the 500 cases here reviewed, I would invite your attention to the particular methods of delivery used, in relation to the time periods in which the cases are grouped. As one would expect, there is a progressive diminution in actual number of cases as time periods lengthen.

Low forceps shows a reasonably constant incidence in all groups, but a general tendency to lessen as the time duration increases. Mid forceps shows a tendency to irregular decrease in incidence as time periods lengthen. A few cases delivered spontaneously after manual rotation, but are so few in number as to not exhibit any trend. Craniotomy also is only occasionally employed, but its percentage does show a sharp climb as time periods lengthen. Spontaneous breech deliveries, breech extractions and versions are too few to exhibit trends in relation to the time. Cesarean sections, both of the lower segment and extraperitoneal types, jump sharply as the time extends beyond the first group. After this the extraperitoneal type of operation exhibits a fairly constant incidence, whereas the transperitoneal type, not so well suited to very prolonged labor, occurs only in small numbers and does not exhibit any constant trend. Extraperitoneal section greatly exceeds our employment of the transperitoneal type in this group. The total number of times this operation was used was forty-one, an incidence of 8 per cent. The total cesarean section incidence was 11.4 per cent. This in relation to cases constituting a specially difficult group is not unduly high.

Cases may be treated conservatively over long periods provided that, in the event of failure of

vaginal delivery, the relatively safe extraperitoneal section may be resorted to. Lacking this resource, many would be sectioned earlier, some of them unnecessarily.

Although we have stated that the weight of the baby is one of the factors which may militate against successful delivery, we find on analysis that there is little regularity of trend in the distribution of weights in relation to the duration of labor.

In relation to gravidity, one finds, as might be expected, that about three-quarters of this group were primigravidae. The age distribution accords with this great preponderance of primigravidae, as nearly 40 per cent of the cases occur in the first five-year period of the third trimester, whereas 83.4 per cent of all cases occur under 30.

We next consider the distribution of the principal causes of difficulty resulting in prolongation of labor. The largest group, amounting to nearly 40 per cent of the whole, depends upon actual mechanical disproportion between the fetus and the pelvis. Others of this group were specified as also complicated by faulty position. We conceive that faulty position in itself depends upon pelvic asymmetry or disproportion. It will thus be seen that nearly 200 of these cases depended upon asymmetry or disproportion as a primary factor.

The second largest group has inadequate quality of the pains assigned as the most important or primary etiology. The third largest group represents combinations of these two primary causes.

Each of the several other causes either originally assigned on the diagnosis sheet or assessed by one of us (C. S. G.) who reviewed the cases, constitutes less than 3 per cent of the total.

Grouping the causes in a slightly different way, it is seen that feto-pelvic disproportion, either alone or in combination with other causes, constituted the etiology of 57.5 per cent of all cases. Inadequate pain quality alone or in combination with other causes was etiologic in 52.2 per cent of the whole.

In the 500 cases, two mothers died, a mortality incidence of 0.4 per cent. This compares with a mortality rate for all the material in our clinic for the same period of 0.28 per cent.

Of the 500 babies, 6 died before the onset of labor, 19 during labor, and 10 subsequent to labor, a total of 35 fetal and neonatal deaths, or a gross rate of 7 per cent. This compares with a gross rate of combined fetal and neonatal deaths for the whole material of our clinic for the period covered by this survey of 6.4 per cent.

From what has been said, it may be stated that:

All obstetric cases at or near term fall into the following groups:

(1) A large majority which deliver spontaneously or with little artificial aid well within a time period approximating the average.

(2) A group in which accidental or complicating circumstances force artificial interference. Such interference is frequently radical and must be employed long before the duration of labor assumes importance. This group includes placenta previa, premature separation, rupture of the uterus, severe toxemia, and other conditions. It embraces the most hazardous situations and accounts for the greatest number of maternal and fetal deaths.

(3) A much smaller group in which obvious mechanical obstruction justifies early elective radical intervention. Here also the duration of the labor is a negligible factor.

(4) An equivocal group in which the most careful prior estimation of delivery potentiality must be tested by an actual trial of labor. This group includes:

(5) A group amounting in our material to 6 per cent of all cases, in which even observation of labor performance is indeterminate until the duration of labor far exceeds the accepted average limits.

It is with the management of the last small, but very trying, group of cases that we are concerned. It may be summarized as follows:

(1) Prophylaxis. — (1) Careful preliminary prognosis based on complete physical examination; supplemented in doubtful cases by roentgenography by suitable technics.

(2) Prenatal observation and regimen especially in reference to control of weight gain and maintenance of muscle-tone by dietary regulation and exercise.

(2) In Labor.—If the course of labor is not characterized by normal acceleration of expulsive powers resulting in progressive evolution toward delivery within approximately average time limit, the case will promise to fall into the group of prolonged labor. Confronted with this prospect, all measures must be intensified to protect the patient:

(1) Against infection (a) by limiting the number of examinations, vaginal or rectal, to a minimum consistent with proper evaluation of conditions and progress.

(b) By specially meticulous technic in making such examinations. For instance, any vaginal exploration should be done in the delivery room, with fullest care, as in actual delivery, in reference to both patient and examiner. Anesthesia is usually advisable.

(2) Against exhaustion (a) by sympathetic but firm effort to allay anxiety and support morale.

(b) By provision of rest by drug sedation.

(c) By maintenance of fluid balance and nutriment. Oral ingestion of plenty of fluids and easily digested nourishment should be encouraged and recorded. If necessary, parenteral administration of water, salt and sugar may supplement ingested substances.

(3) Against hemorrhagic risk (a) by blood typing. This may readily be included in regular prenatal routine. It should always be done in the presence of potential difficulty.

(b) Provision of donors in advance of need of them, and of facilities for making blood from them quickly available.

(c) Provision of instantly available substitute liquids for intravenous use in presence of hemorrhage or shock.

In his approach to the cases, the mental attitude of the obstetrician should be governed by such considerations as:

(1) That time elapsing from the beginning to the end of labor is *per se* of little importance, provided the patient can be protected as already indicated.

(2) That greatest danger in these cases depends on impulsion to interfere before conditions for such interference are ideally fulfilled.

(3) That time is his own greatest ally. If he has the proper resources at command, delay will rarely be against his patient's interest. It will very frequently solve or simplify his problem.

Imbued with this attitude, he will, in addition to the protective management outlined:

(1) Carefully recheck, in all its details, both the physical examination and previous preliminary prognosis.

(2) On this basis, endeavor to assess the cause or causes of delay.

(3) And determine, if possible, the probable channel of delivery.

At this point procedure will necessarily vary with conditions.

(1) If the obstetrical attendant have at his command procedures limited to the vaginal route he can only, and must wait until:

(a) The cervix is fully dilated and retracted completely around the head.

(b) And the biparietal plane of the head has passed the inlet. It is important to remember here that in heads well molded, as they generally will be in these cases, the most dependent part of the skull itself (not merely the caput) will be well down on the pelvic floor.

Time, time and more time should be availed of to insure fulfilling these conditions. Occasionally a baby will succumb. This must be accepted. But unless these restrictions are religiously adhered to, the chances are great not only of losing the baby, but of seriously jeopardizing the mother.

The resources for vaginal delivery in such situations are almost entirely the forceps. While version, as a matter of some experience, has resolved difficult situations, it must in general be assessed as fraught with much danger to both mother and child.

Posterior pituitary extract or similar products are almost never to be used before the end of the second stage. If they are, conditions similar to those for forceps must be fulfilled. Utmost caution and fractional dosage must always be used.

Manual or instrumental dilatation of the cervix has no legitimate place in obstetrics. It always causes, or tends to cause, laceration. Lacerations are always potentially dangerous.

Only very, very rarely is incision of the cervix necessary or justifiable. If used, anterior and posterior incisions, with mobilization of the bladder, are preferable to Dührssen's incisions.

In cases of intrapartum fetal death, craniotomy is sometimes a conservative measure.

(2) If the attendant have at his command, in addition, classical cesarean section only:

Decision to resort to abdominal delivery is fixed with reference to the duration of labor and the time of rupture of membranes.

If this operation is to be resorted to, it should be done preferably within 24 hours of onset of labor and within 6 to 8 hours of rupture of membranes.

Mortality and morbidity rates increase rapidly after these limits. If they cannot be respected, do not do the operation. Craniotomy is a preferable alternative.

(3) If low cervical cesarean section is available, approximately the same restrictions obtain as apply to the classical type. While definitely preferable to the latter, it is still a transperitoneal approach. It must not be depended upon to protect against infection.

If vaginal delivery even by craniotomy is absolutely impossible, and transperitoneal approach must be used under unfavorable conditions, the uterus should be extirpated by the modern Porro technic.

(4) Finally, the obstetrician may have at his command extraperitoneal cesarean section. There are several available types:

(a) Exclusion operations as those of Hirst and your own Cooke. These are not considered as desirable as,

(b) True extraperitoneal section as by the Latzko technic, or

(c) Best of all, the supravesical approach developed in our own clinic by Waters, shortly to be published.

Armed with such complete resources, the well qualified obstetrician may permit his patient to remain in labor, properly protected until ample time has elapsed to demonstrate fully the inadvisability of vaginal delivery. Resort may even then be had to extraperitoneal section without inordinate risk.

My discussion, of course, has been concerned principally with the hospital management of cases. It must be recognized that if proper hospital facilities are not available, higher maternal and fetal morbidity and mortality must to a certain extent be accepted. However, the general principles outlined as applied to hospital practice with the exception of the more radical operative procedures may and must be applied to cases no matter where handled. If obstetric material is cared for outside of the hospital there is nothing in the management proposed which may not be applied by the conscientious and competent obstetrician. It is especially under such circumstances that the need for time to permit spontaneous evolution of natural labor is the more necessary and imperative.

CONSIDERATIONS IN EVALUATING THE THERAPY OF HAY FEVER*

By CHARLES H. EYERMANN, M.D.†
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In hay fever, the severity of the symptoms and the intensity of the complaint is due to the variety of factors activated by the absorption of pollen; they are never alike in any two individuals nor alike in the same individual at different times, and since there is no method of gauging or depicting the severity of symptoms or of proving the efficacy of therapy by impersonal means, so that all physicians could measure alike, the reports upon therapy, perforce, are the personal opinions formulated by physicians from the statements of patients.

It is the purpose of this communication to indicate the factors which should be considered in determining the efficacy of any therapy for hay fever.

(1) The amount of pollen absorbed, which is dependent upon:

(a) Meteorologic conditions.

(b) Auto-inoculation.

(c) Personal factors.

(2) The degree of sensitivity of the patient.

(3) The additive effect of allergen other than pollen.

(4) The psychic reaction of the patient to discomfort.

(5) The irritant effect of intranasal therapeusis.

Meteorologic influences upon the growth of plants and the distribution of their pollen are the most important of these factors. Since these influences are not static or exactly repetitious from year to year, it is impossible for us to know how much more or less pollen will be available for absorption from year to year and therefore impossible to know in advance the amount of medicinal or biologic therapy necessary for the palliation or cure of the disease.

In general, the severity of symptoms is in ratio with the number of grains of pollen found on pollen slides. When one analyzes each patient separately, however, there are many in-

*Chairman's Address, Section on Allergy, Southern Medical Association, Thirty-Third Annual Meeting, Memphis, Tennessee, November 21-24, 1939.

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stances in which the peaks of a pollen graph made from the fall of pollen at only one place do not correspond to the periods of severer symptoms. One can assume that one cause of this divergence is the amount of pollen in the air in the patient's immediate environment, for graphs made from the fall of pollen at different locations in the environs do not correspond in the number of pollen grains found, and many times there is dissimilarity in the peaks and depressions of the graph. For example, this year in St. Louis a few ragweed pollen were found as early as July 4 by Mr. O. C. Durham on his slides exposed at a height of one hundred seventy-five feet, with no interference to the wind, at the United States Weather Bureau, located in the business district; they were found on July 15 by Dr. French K. Hansel at an approximate height of one hundred thirty-five feet, with north, east and west exposure, and by myself on July 19 at an approximate height of one hundred twenty-five feet, with east and south exposure at a location about three miles west of the station at the weather bureau. This was the earliest time, in my experience, that ragweed pollen was found on slides and a survey of vacant lots found a few ragweed plants in bloom in the heart of the city. Obviously, persons susceptible to ragweed pollen living in that immediate vicinity would have some degree of symptoms and presumably have them of some degree over a longer period of time. A comparison of the graphs made from these counts shows a great difference in the total pollen counts, and while the peaks correspond on the days with the highest count, there are many days with the reverse: theoretically, an influence upon the severity of symptoms of patients in that locale. The possible multiplication of such instances must be remembered in compiling statistics.

Rain ameliorates the symptoms in most people, but its effect on the pollen graph is not so striking. Surprisingly large amounts of pollen are found on slides exposed for twenty-four hours during which there has been a heavy precipitation of short duration. Such rains apparently affect the atmospheric density of the pollen at the time it is raining, and decrease the amount of pollen found on slides for only twenty-four hours, so that we have the paradox of relatively mild symptoms in certain individuals at periods of relatively high counts. Here again, the severity of the symptoms probably depends upon the patient's location in respect to the rainfall. In the St. Louis district, one has access to the reading of eleven rain gauges from two to fifteen miles apart. It is usual to have different readings on all the gauges and it is not infrequent to have rainfall registered on some of them only (experience this year with an inch of rainfall in one section of the city of St. Louis, but a registration of only 0.01 inch at the Federal Building, a distance of five miles away). Therefore, it is possible that patients living in one portion of the city have very few symptoms, while on the same day others living in other parts will have severe symptoms, a possibility to be considered in the evaluation of therapeutic results.

While rain ameliorates the symptoms in most people, in others it increases the nasal blockage, a blockage indistinguishable by the patient from that which occurs from the absorption of pollen. In such individuals the blockage should not be attributed to the direct effect of pollen, but from the standpoint of the questionnaire will appear as evidence detrimental to the therapy employed, another possibility to be considered in the evaluation of therapeutic results.

Wind is another element which appears to influence the intensity of clinical symptoms, but when wind velocities are superimposed on pollen graphs, corresponding increases in pollen counts are not always present. The climatologic situation which brings about the highest pollen count and the severest symptoms is the occurrence of winds of high velocity during the period of most active pollination. The unexpectedly high pollen counts during periods of rainfall, undoubtedly, are due to the increased wind velocity preceding and often succeeding precipitation. Probably wind velocities of low rates during the height of the pollen period are as potent in inducing intense hay fever symptoms as are high velocities either in the beginning or end of the season.

Pollen graphs made from the fall of pollen at one place are only an index of the symptoms of the group under observation, but they are not reliable when each individual is considered separately. The applicability of such graphs to the clinical situation is more that of an indicator of the first appearance and ultimate disappearance of pollen than that of an estimator of the pollen concentration in the air. As long as pollen appears on pollen slides, the potentiality exists for some to have symptoms of varying intensity, and knowing the possible dose of pollen is only a part of the data required to determine the value of a therapeutic measure.

By auto-inoculation is meant the tendency of all patients to rub their eyes and compress and rub their nose, thus compelling additional absorption of pollen and thereby increasing the severity of their symptoms. The effect of pollen is the same, whether absorbed from a hypodermic injection or from a mucous membrane into which it has been forcefully rubbed or compressed. In my experience, many patients have considered themselves more comfortable when they have voluntarily restrained the impulse to rub, and used simple measures for the quick removal of pollen from the mucous membranes.

By personal factor is meant those things that happen in a patient's existence which he forgets to tell the physician because he does not know or believe have an influence on the course of his symptoms or because he wants to believe that the instituted therapy has been helpful. Insistent and adroit questioning is often necessary to bring out such information. As crude examples, I would cite the patient who had had preseasonal injections for several years with definite improvement, but with some hay fever symptoms present most of the time. He, then, has an excellent season, but the conclusion that this delightful therapeutic result is due entirely to pollen therapy in the presence of a high total pollen count is vitiated by the educed information that he worked in a meat cooler from 2:00 p. m. to 10:00 p. m. each day. Again, an out-of-town patient with hay fever and asthma, treated by his family physician under our direction, was reported by him to have had neither hay fever nor asthma. Some months later the patient made me a congratulatory visit and I elicited that he had been housed during the period of greatest pollen concentration, by an intercurrent illness, which altered the statistics and cast another doubt on the reliability of questionnaires.

Our percentage of excellent and good results from pollen therapy has been a little higher since 1930, which we should like to attribute to improvement in the technic of pollen therapy; but the fact that many of those in whom improved results have been obtained do not visit the golf clubs in the country as often as formerly, or now work in air-conditioned offices, casts a doubt upon the pollen therapy as being the sole reason for the improved clinical results. Perhaps in this group one should also include patients who consider themselves as having an excellent result without specific therapy, whom we might classify as controls. As examples of diverse and nonspecific therapies, I saw a 13-year-old boy, on the 25th of August, in his fifth year of hay fever. He was advised as to the means of avoiding contact with excessive amounts of pollen, given 0.2 per cent solution of ephedrine hydrochloride for instillation in the eyes when necessary, and one-quarter grain of ephedrine hydrochloride, orally, three times a day. Another patient, an adult in the fifties, in the twelfth year of hay fever, was given the same advice as to avoiding contact with excessive amounts of pollen and a teaspoonful of elixir of sodium bromide, three times a day. Despite the fact that the total pollen count was higher than usual, both these patients reported a better season than they have ever had.

Of course they would have reported the same thing with any other type of therapy, and one can assume that for some reason these patients absorbed less pollen than usual despite a potentially severe season. But a similar result has been obtained without medicinal or immunologic therapy. In 1919, a lad was observed with spring hay fever, skin sensitive to grasses. Advice as to the manner of avoiding contact with excessive amounts of pollen was the only treatment. He had no further symptoms until the spring of 1935; again no specific treatment was given; he has had no hay fever symptoms up to the present time, and the positive cutaneous reactions to the grasses are still present, and now he is sensitive also to ragweed. Certainly this is a good to excellent result for any therapy. One wonders if this clinical course occurs often enough to influence our statistics on therapeusis. When one deliberately treats a group of patients by nonspecific therapy each year, similar examples occur often enough to make it advisable to withhold judgment as to the worth of any therapeutic procedure until repeated on the same patient for at least five years.

Patients who travel present difficulties for the statistical evaluation of therapeutic results. Certainly those who receive hyposensitization injections and go to districts where the offending pollen does not exist, should not be included in any statistics. In particular, I refer to those patients who have considered themselves well, as the result of pollen therapy, in their native cities where the pollen count is high, who are quite uncomfortable in cities with low pollen counts, and also the reverse, all at comparable

periods: a situation difficult to explain on the vagaries of any therapy.

The cutaneous reaction to serial dilutions of pollen solutions is the accepted method of determining the degree of sensitivity. It appears logical to assume that those who give a cutaneous reaction to the weakest solution will have noticeable discomfort from the absorption of small amounts of pollen and it is the consensus that it is more difficult to obtain a satisfactory therapeutic result in those who have cutaneous reactions to the weakest pollen solution. But discrepancies occur between the complaint and the immunologic reactions. Only too frequently are severe symptoms present in those with small cutaneous reactions and large reactions in those with mild symptoms. Perhaps these are examples in which the intensity of the symptoms is determined by the psyche or is mediated by meteorologic influences on the body, as those who are worse with damp weather, low temperature, and so on. The evaluation of therapy would be more accurate if its effect were reported in relation to the gradations of skin sensitivity, to meteorologic influences upon the body and to the temperament of the patient.

It is generally agreed that some of the patients unaffected by specific treatment become so when they avoid the absorption of allergen other than pollen. That this favorable result may not be due entirely to the specific treatment is intimated by a small number of patients with seasonal vasomotor rhinitis and positive cutaneous reactions to the pollen in the air at the time of their symptoms, but comfortable to their own satisfaction by merely avoiding foods. As striking examples I would cite two patients under observation for twenty years who have had a satisfactory ragweed season by not eating corn, and a patient under observation for ten years who is comfortable by not eating any member of the bean family, and a fourth, who had seasonal vasomotor rhinitis and asthma despite prophylactic injections which reached a maintenance dose of 0.50 c. c. 1:50 dilution of ragweed solution, who promptly improved with a trial diet.

The avoidance of inhalants other than pollen also brings about a satisfactory therapeutic response in those who have seasonal symptoms. In our experience about 5 per cent of the patients who visit us during the hay fever season under the impression that pollen is the cause of their complaint are found sensitive to orris root; in a smaller percentage of similar instances the symptoms are due to animal epidermals, cottonseed and unusual pollen. These examples are cited, not for their vividness, but for emphasis upon the possibility that such factors may be unwittingly and accidentally avoided, thus crediting the instituted therapy for the relief of symptoms rather than the real reason. And, now one considers the molds as important allergens during the pollen seasons, either as dominant or additive factors. They, too, can be unwittingly avoided or be less abundant, thus accounting for a good result attributed to the instituted therapy.

The psychic reaction of different individuals to the same type of discomfort is never the same, but in hay fever, probably because of the inherited significance of respiration, the disproportion between the emphasis upon the severity of the affliction and its identifiable evidence, is frequent and striking. One must be ever on guard for an exaggeration of the complaint, for psychogenic coloration, or for overvaluation of symptoms. One is so likely to forget that the emotional make-up, the human factor present both in the patient and in the physician, interferes with accurate appraisal of the clinical situation. Bohner* has expressed it well:

> "That any statistical report can be anything more than an approximation cannot be denied. The patient whose symptoms are those of sneezing, mild nasal blockage, and lacrimation will be dissatisfied with anything less than 100 per cent results. The patient who has had to spend three weeks in bed because of severe pollen asthma is enthusiastic if his symptoms are relieved to the point where he is able to carry on his usual occupation, even though he may have daily attacks of hay fever or asthma. The doctor is disappointed in the treatment, but not the patient. The results reported are a combination of the patient's disappointment or overenthusiasm and the doctor's dissatisfaction or overestimation."

The use of intranasal therapeusis introduces another difficulty in evaluating the worth of any other therapy. Not only because several therapies are being used simultaneously, but also because intranasal medication has a tendency to increase the already existing discomfort, thereby invalidating the effect of any other therapy. The patient meanwhile is more likely to believe that the severity of his distress is increased because of the ineffectiveness of the ancillary therapy. Certainly those who have had hay fever for many years know that they are more comfortable with the absolute minimum of intranasal medication and this ideal situation should

*Bohner, C. B.: Jour. Ind. Med. Assn., 31:279, 1938.

be attained before coming to conclusions as to the worth of other methods of therapeusis.

One of the most difficult problems in medicine is the evaluation of therapeutic measures which are not susceptible of proof, either by animal experimentation, by laboratory procedures, or by carefully controlled morbidity and mortality studies, and which rest for their acceptance on an empiric basis. This is particularly difficult in hay fever because the severity of the symptoms is dependent upon an agent not only of quantitative and durational variation from day to day and from year to year, but also upon one provoking many interrelated and interdependent personal factors which puzzle the clinical picture. It is natural to attribute improvement to the remedy being used at the time, but patients are uncertain witnesses for themselves and the statement as to how the patient feels is influenced by the most recent phase of his affliction and by his state of mind, whether of hope or discouragement. Of necessity, treatment must be experimental, and since there is a great deal of difference between betterment and cure, and since cure is not accomplished easily, readily, or rapidly, while improvement is a matter of personal opinion, one in which the patient and the physician must be in agreement, the report of the efficacy of any therapy should be the results of five years' observation on the same patient, having due regard for the influence of the daily, seasonal and local fluctuation in pollen density and variations in the length of pollen production on treated as well as comparable untreated patients.

SUMMARY

Before assuming that a given therapy is moderating the symptoms of hay fever, one should ascertain that this improvement is not due to lessened absorption of pollen as the result of meteorologic influences upon the growth of plants and the distribution of their pollen or by such other factors as the unwitting avoidance of pollen and allergen other than pollen, one or both, at the same time having due regard for the influence of the immunologic degree of sensitivity, the psychic reaction to discomfort, and the irritant effects of intranasal therapeusis upon the severity of the symptoms.

CONCLUSIONS

Because of the unpredictable variation in the production and the distribution of pollen and because of the variable response of affected persons to the absorption of pollen, it is counseled that a given therapy should be applied to the same patient and evaluated in relation to the factors known to influence the symptomatology over a period of five years before concluding as to its worthiness as a therapeutic agent.

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ROUTINE TUBERCULIN PATCH TESTING IN INFANCY

By Lee Bivings, M.D.
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For a long time it has seemed advisable that routine tuberculin tests should be made on all infants near the end of their first year, because of the prevalence of tuberculosis among the negro race, which furnishes the greater number of nursemaids.

It was not until 1937 that a commercially available form of painless testing could be had when Vollmer and Goldberger[1] introduced the patch test. Since their first report there have been several other reports in which the reliability of the test has been compared with old tuberculin intradermally and purified protein derivative. *Table 1* shows the findings of these other workers.

Table 1

COMPLETE CORRELATION

Author	No. Cases
Hart[2]	536
Vollmer and Goldberger[3]	678
Taylor[4]	744
Steward[5]	96
Total	2054
Ninety-Five Per Cent Correlation	
Wenger and Neustadt[6]	257
Serious Lack of Correlation	
Peck and Wegman[7]	880
Patch negative PPD I positive	55
Patch positive PPD I negative	18

*Read in Section on Pediatrics, Southern Medical Association, Thirty-Third Annual Meeting, Memphis, Tennessee, November 21-24, 1939.

It would seem, then, that the patch test can be accepted, with a small percentage of error, as equal in reliability to that of 0.1 mg. old tuberculin intradermally or lesser dilutions. For the purposes sought in this study it seems likely that most cases of infection are ruled out by the negative patch test, although it is fully realized that in any cases of suspected tuberculosis it would be necessary to test with 1 mg. old tuberculin before the case could be considered free of infection.

This study was undertaken to determine whether infection in early life might occur more frequently than has been suspected. Beginning November 1, 1938, routine tests were done on all private patients under routine care just before they reached their first birthday; also included were a few older children, most of whom were in their second year. The data were kept until November 1, 1939, and included exactly one hundred cases.

There were ten positives, all of which occurred in children under one year. Thus ten per cent of this group had been infected with tuberculosis by the time the infants were one year old. Since all were in good health, the factor of greatest importance was to find the source of infection in as many as possible. This was done in three instances; one was proven to have been infected by a negro maid, and two others, brother and sister, were found to have been exposed to a friend who, unknown to the parents, had active tuberculosis and had played with the children on many occasions.

In the remaining seven the sources of infection could not be traced but it is highly probable that in most of the cases the infection came from negro maids who, changing often, could not all be examined for tuberculous activity.

It would seem, then, that if tuberculosis has occurred in ten per cent of babies coming from good homes and healthy parents, that this is a servant hazard far greater in importance than that of venereal diseases, about which much has been said in recent years. I have never known a case of either gonorrhea or syphilis which was transmitted to a child by a negro maid, but I have known of several cases of tuberculosis thus transmitted, one of which resulted in tuberculous meningitis and death.

DIFFICULTIES IN PATCH TESTING

I have observed irritation in a few instances from applying the test before the acetone had evaporated, which gave a severe irritation under the whole of the patch and made reading impossible. Only one child pulled the patch off. The patches were put on between the scapulae where it was difficult to reach them. A few showed only enough irritation under the tuberculin-containing patches to make it difficult to read them; these tests were repeated with only one out of five proving positive.

SUMMARY

Tuberculin patch testing is simple, painless, and accurate to the same extent as 0.1 mg. old tuberculin (Mantoux). Its adoption as a routine in the care of all infants reaching one year would uncover many hitherto unsuspected sources of tuberculous infection.

It should not be regarded as final evidence when negative, but should be followed by 0.1 mg. old tuberculin intracutaneously in suspected cases.

Because of its simplicity and safety and lack of pain it would make an excellent substitute for the primary test in all cases.

CONCLUSIONS

Tuberculosis would seem a much greater hazard to the healthy infant than venereal disease from contact with negro nurses. In the care of infants, patch testing offers a simple, reliable and painless method of detecting unsuspected infection, especially from nurses. If infection is discovered, the source of infection can frequently be traced, and reinfection from that source prevented.

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DISCUSSION (*Abstract*)

Dr. W. P. Dearing, Montgomery, Ala.—Tuberculosis workers have long been studying and using various types of tuberculin and methods of application. The fact that many preparations and technics have been tried and that new ones are still being developed is *prima facie* evidence that there is no entirely satisfactory preparation or method of testing. Part of the confusion results from the comparative simplicity of the test, which has resulted in the attaching of unwarranted significance to its results. There is a temptation to extend the significance of the test to definitive diagnosis and prognosis instead of remembering that it is a biological phenomenon subject to wide variations. A reaction to a given dose of tuberculin means nothing of itself; clinical significance can be attached to it only in the light of other facts obtained by careful study.

When we undertake to use a tuberculin test, therefore, we should give careful consideration to our purpose. Tuberculin has many uses. It is used for treatment; it is used in "screening" for case finding; it is used for differential diagnosis of pulmonary conditions; it is used, some of us think overused, for something we vaguely call its educational value, and Dr. Bivings presents its use as an indirect means of finding cases in adults.

Dr. Bivings finds the patch test to agree fairly well with one of the commonly administered intracutaneous tuberculin doses. Peck and Wegman (*Journal of Pediatrics*, 15:219, August, 1939) found 24.4 per cent of 225 patch-negative school children reacted to 0.00002 mg. of PPD and 9.6 per cent of 188 PPD negative children who were patch-positive. These findings suggest that the two tests do not necessarily always measure the same thing. Dr. Bivings might have found more discrepancies in a larger series. The conclusion remains, however, that the method of choice must be left to the practitioner, and the patch test has some advantages for office practice. For comparative testing of large groups, however, the patch test cannot be considered established as statistically comparable with the Mantoux method.

Finally, with regard to Dr. Bivings' emphasis on the examination of adult contacts of reacting children, I would submit that the pediatrician's responsibility for preventing tuberculosis in his patients would be better met by insisting on routine chest x-ray examination of the adults around the child, especially the asthmatic aunts and colored maids, than by relying on a tuberculin test to tell him the horse has been stolen so that he may then lock the door.

Dr. Clyde V. Croswell, Memphis, Tenn.—Inasmuch as tuberculosis still ranks as one of the leading causes of death and disability, we physicians should work more diligently to eradicate it, since it is a preventable disease.

In my experience, the patch test is approximately as accurate as the test done with 0.1 milligram dilution of old tuberculin. Routine testing by the patch method has its advantage, because of the fact that the public will accept this method, whereas many mothers object to their children having to be tested by being stuck with a needle. Routine testing facilitates the tracing and locating of the source of the primary infection and, in turn, allows one to isolate the patient from the infected individual.

The question was brought up of examination of colored maids or nurses. I will grant you this: tuberculosis is not picked up very easily in the early stages, even with x-rays and with thorough examinations. A statement that the colored maids are all right does not necessarily relieve me or convince me that they are not possible carriers or may not infect the children with tuberculosis. I have had several cases directly due to colored maids. I have had one or two in which, after I got a positive test, the parents denied any infection and did not believe it. They did not want to go any further. In one of the positive cases, in less than two weeks the maid had a severe hemorrhage, and the parents were easier to control from then on. Before that time they doubted that there was infection in their family. Most of the maids do not go for a routine examination, and if they do go they probably are not examined by those capable in many instances of picking up tuberculosis.

It has been my experience that unless these individuals are separated the primary infection often results in a secondary infection, and the patient frequently comes with miliary tuberculosis or tuberculous meningitis. I have had one or two patients who stayed in a home where they knew there was infection. We tried to isolate them. These have usually died either with tuberculous meningitis or with miliary tuberculosis.

This test allows one to detect the source of infection before the fatal type develops. The infected adult ordinarily does not readily submit himself for examination until he has spread the disease and infected others. If the test is done annually you will often pick up infection before it has perhaps caused fatal damage. It is about the best method of finding and preventing the spread of tuberculosis. We physicians can educate the public to routine tuberculin tests. It is essential that each of us cooperate in teaching the public the value of these tests.

Is the test harmless? In my mind, the amount of information gained and the results obtained far outdistance anything that might have been caused from testing, that is perhaps the flaring up of an infection.

Dr. Bivings (closing).—One of the things that made the patch test particularly applicable, it seems to me, to this particular study was the fact that it is very probable that a negative test obtained by the patch method in an infant of 1 year or 11 months or so would be much more important than perhaps it would later on. In other words, one would have reason to believe that a negative test in this particular age group would come nearer screening out those children who had been infected with tuberculosis than if one were done later on at, we will say, the age of 5 or 10 or any other later age. There is no doubt that there is no perfect method. Each method has its disadvantages, but it seems to me for this particular purpose in private practice the patch test is far ahead of any of the others up to the doses discussed; that is, 0.1 milligram of old tuberculin or the fresh dilution of the PPD. In suspected cases it certainly could not be considered final in trying to eliminate a suspected case of tuberculosis.

I have just discussed the fact that the relative comparative dosage is such that one could not consider the patch test effective in cases that would not respond to the 0.1 milligram dosage, and it has been shown in many instances—I have some figures here from the State Department of Health—that the tests of school children showed about twice as many children with the 1 milligram dilution as with the 0.1, so we cannot feel

that it is final if we get a negative with 0.1 milligram. Of course it is impossible to examine all contacts for the young baby. It is much easier to try to find whether or not the baby has been infected, and if he has, then find who did it.

An annual application of the test would, of course, be very useful, although it seems to me the danger period is during the first year. As far as I have been able to determine, the patch test apparently is harmless. So far, there have been no cases of tuberculosis stirred up by doing a patch test, but in, I think, the November issue of the *Journal of Pediatrics*, no doubt some of you have seen the report in which there was active involvement of tuberculosis, stirred up by even 0.1 milligram of old tuberculin intradermally. For our own purposes in routine work in private practice, the patch test is far more useful than any other method we have had.

RECENT STUDIES OF EPIDEMIC DIARRHEA AND DYSENTERY*

By ERNEST L. STEBBINS, M.D.
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Dysentery has been a reportable disease in New York State since 1914, but it was not until 1928 that a distinction was made in morbidity reporting between bacillary dysentery and amebic dysentery. Report of diarrhea and enteritis has not been required, except when they occur in epidemic form. In the past it has been general practice in New York State as elsewhere, with the exception of cases occurring in common source epidemics, to report as bacillary dysentery only those cases showing the so-called typical clinical syndrome, including gross blood and mucus in the stools. That infection with pathogenic varieties of the *B. dysenteriae* group may be associated with mild symptoms and the absence of blood or mucus in the stools is well established. For this reason, reported morbidity almost certainly grossly understates the prevalence of infection. It seems probable, however, that because of a gradual increase in the use of diagnostic laboratory procedures, the basis of reporting morbidity has changed somewhat in recent years.

In view of the similarity in the method of transmission of typhoid fever and bacillary dysentery, it might be expected that with the improvements in environmental sanitation which have resulted in a marked reduction in typhoid fever there would be a parallel reduction in bacillary dysentery. Reported morbidity in New York State has not indicated such a reduction, but rather an increase not only in epidemic but also in endemic dysentery. This increase is probably the result of a more general use of laboratory methods in diagnosis with more complete reporting, rather than an actual increase in morbidity.

Table 1

REPORTED TYPHOID FEVER AND BACILLARY DYSENTERY NEW YORK STATE,* 1928-1938, EXCLUSIVE OF EPIDEMICS

Year	Number of Cases		Attack Rate per 100,000 Population	
	Typhoid Fever	Bacillary Dysentery	Typhoid Fever	Bacillary Dysentery
1928	506	45	11.5	1.0
1929	479	113	10.8	2.5
1930	510	151	11.3	3.3
1931	457	86	10.0	1.9
1932	376	103	8.2	2.2
1933	316	100	6.8	2.2
1934	288	122	6.2	2.6
1935	272	136	5.8	2.9
1936	186	129	3.9	2.7
1937	227	266	4.7	5.6
1938	173	282	3.6	5.8

As shown in Table I, there has been a continued decrease in reported typhoid fever but an increase in reported dysentery. The consistently increasing recognition of bacillary dysentery would seem to indicate that this disease is a more important public health problem than it has sometimes been considered. The importance of bacillary dysentery is, moreover, indicated by the accumulation of evidence that even extremely mild attacks of this disease may be followed by chronic sequelae not obviously associated with the acute illness, but apparently due to infection with *B. dysenteriae*. For this reason, epidemiological studies of both endemic and epidemic dysentery seem indicated.

ENDEMIC DYSENTERY IN NEW YORK STATE

Bacillary dysentery is endemic in this area as evidenced by the occurrence of sporadic cases in all sections of the state. Sporadic cases are rarely reported except upon bacteriologic confirmation of the diagnosis and not infrequently case reports are withheld by physicians if no blood is observed in the stools, even when labora-

*Read in Section on Public Health, Southern Medical Association, Thirty-Third Annual Meeting, Memphis, Tennessee, November 21-24, 1939.

*Exclusive of New York City, Buffalo, Rochester, Syracuse, and state institutions.

Table 2

ENDEMIC BACILLARY DYSENTERY ACCORDING TO TYPE BY POPULATION GROUPS, NEW YORK STATE,* 1938

Population Group	Population as of July 1, 1938	No. Cases			Rates per 100,000 Pop.		
		Flexner	Sonne	All Forms	Flexner	Sonne	All Forms
50-250,000	849,166	—	4	8	—	0.5	0.9†
25-50,000	373,033	2	1	14	0.5	0.3	3.8
10- 25,000	757,593	16	11	41	2.1	1.5	5.4
2,500-10,000	633,006	15	5	23	2.4	0.8	3.6
Under 2,500	2,213,735	70	105	196	3.2	4.7	8.9
Over 2,500	2,612,798	33	21	86	1.3	0.8	3.3†
Under 2,500	2,213,735	70	105	196	3.2	4.7	8.9
Total	4,826,533	103	126	282	2.1	2.6	5.8

tory examination reveals the presence of *B. dysenteriae. B. dysenteriae Sonne* was the type most frequently encountered among the sporadic cases reported during 1938, but as shown in Table 2 organisms of the Flexner group were encountered with almost equal frequency. Schmitz bacillus was isolated from a relatively small proportion of cases and has been observed only in hospitals for the insane. *B. dysenteriae Shiga* has not been found to be the etiologic agent in cases occurring among residents of the state. As seen also in Table 2, endemic dysentery due to both of the common types of dysentery organisms was most prevalent in rural areas and small villages. There was a significantly higher attack rate in the population group under 2500 for all types and for each of the common types. This distribution of cases by population groups is similar to that observed in endemic typhoid fever in New York State, as shown in Table 3. As elsewhere, water purification is generally more adequate, sewage disposal is more carefully regulated and milk pasteurization more general in the larger cities.

The age distribution of endemic dysentery differs slightly from that observed in typhoid fever. Attack rates for dysentery are higher among young children than among adults. As shown in Table 4, the largest proportion of cases of endemic bacillary dysentery occurred in the age groups 0-4 and 5-9, while the proportion of cases in the age group 10-20 is low. More than 50 per cent of all the cases occurred in persons under twenty years of age.

The seasonal distribution of sporadic cases of bacillary dysentery in New York has not been different from that observed in other places. As shown in Table 5, approximately 60 per cent of the cases reported during 1938, exclusive of epidemics, occurred in the three months' period July through September.

Table 3

ENDEMIC TYPHOID FEVER AND BACILLARY DYSENTERY MORBIDITY BY POPULATION GROUPS IN NEW YORK STATE*

Population Group	Rates per 100,000 Population	
	Typhoid Fever Average 1933-37	Bacillary Dysentery 1938
50-250,000	3.0†	0.9†
25- 50,000	4.9	3.8
10- 25,000	4.7	5.4
2,500-10,000	5.2	3.6
Under 2,500	7.1	8.9
Over 2,500	4.3†	3.3†
Under 2,500	7.1	8.9

Table 4

ENDEMIC DYSENTERY BY AGE, NEW YORK STATE,‡ 1938

Age Group	Cases Reported	Per Cent of Total
0-4 years	62	22.2
5- 9 years	54	19.4
10-14 years	21	7.5
15-19 years	15	5.4
0-19 years	152	54.5
20-39 years	60	21.5
40-59 years	46	16.5
60 years	21	7.5
Total	279	100.0
Not stated	3	

EPIDEMIC BACILLARY DYSENTERY IN NEW YORK STATE

As previously stated, diarrhea and enteritis are not notifiable diseases in New York State except when occurring in epidemic form. It has long been known that a large number of diarrheal outbreaks occurred each summer, especially in the resort areas. There is considerable evidence

*Exclusive of New York City, Buffalo, Rochester, Syracuse, and state institutions.

†Exclusive of Syracuse.

*Exclusive of New York City, Buffalo, Rochester, and state institutions.

†Exclusive of Syracuse.

‡Exclusive of New York City, Buffalo, Rochester, Syracuse, and state institutions.

Table 5

SEASONAL DISTRIBUTION ENDEMIC DYSENTERY NEW YORK STATE,* 1938

Month of Onset	Number of Cases	Per Cent of Total
January-March	10	3.6
April-June	21	7.4
July-September	166	58.9
October-December	85	30.1
Total	282	100.0

that even rather widespread outbreaks occasionally were not reported to health authorities. With the elaboration of the district system of local health administration in New York State, an increased staff of trained personnel has been available to investigate diarrheal outbreaks. As a result, there has been a marked increase in the number of outbreaks recognized and reported.

In the past, in a considerable proportion of epidemics, a specific etiologic agent has not been determined, and for the most part these have been designated as epidemics of gastro-enteritis. This term has frequently been used rather loosely, but in recent years has been applied only to outbreaks in which nausea, vomiting and diarrhea were prominent symptoms and in which no known pathogenic organism was found to be the etiologic agent.

With more adequate personnel for investigation of epidemics and rumors of epidemics, the number of diarrheal outbreaks reported has increased markedly. In 1936, 27 epidemics, including approximately 1,100 cases of diarrheal disease, were reported and studied. In 1937, 48 such epidemics are known to have occurred, including approximately 1500 individuals. In 1938, 72 epidemics of diarrhea were reported, comprising approximately 3,300 cases. This marked increase in the number of epidemics reported is not believed to have indicated that there was an actual increase in the prevalence of diarrheal disease, but rather more frequent recognition of this condition.

During the past few years, special efforts have been made to provide for prompt and complete investigation of such outbreaks. Sanitary code regulations requiring immediate notification of outbreaks of diarrheal disease to the district state health office have been enforced. Insofar as possible, complete epidemiologic investigations have been made and bacteriologic studies instituted promptly. It is believed that as a result of the more prompt investigation of these outbreaks an increased number of epidemics have been found to be bacillary dysentery. As shown in Table 6, eight epidemics of dysentery were recognized in 1936, 12 in 1937, and 20 in 1938.

Table 6

EPIDEMICS OF PROVEN BACILLARY DYSENTERY NEW YORK STATE,* 1932-1938

Year	No. of Epidemics	No. of Cases
1932	0	0
1933	3	44
1934	2	41
1935	2	154
1936	8	275
1937	12	352
1938	20	1018

The severity of illness differs considerably in different individuals in the same epidemic and in different epidemics due to the same type of organism. Comparison of the severity of illness in different epidemics is difficult, but most of those engaged in the investigations agree that in general, illnesses due to infection with the organisms of the Flexner group are more severe than those due to the Sonne or Schmitz varieties. Table 7 shows the epidemics studied according to the type of organism found to be the etiologic agent.

An unusually large proportion of the population of the state is regularly supplied by municipal water supply systems. In 1938, there were 807 public water supplies serving approximately 12,000,000 people or 90 per cent of the population. These supplies are inspected and treatment supervised by the engineering staff of the Department of Health. It is notable that no epidemic of typhoid fever traceable to a public water supply has occurred since 1928. An epidemic, consisting of 141 cases of diarrhea of unknown etiology in which a public water supply was believed to be the vehicle of infection, occurred in 1937. A public water supply is believed to have been responsible for an outbreak in 1938, consisting of 84 cases of bacillary dysentery. Epidemics of diarrhea and dysentery, however, rarely occur in well established communities.

During 1938 prohibition of the sale of milk other than pasteurized or certified milk or its

*Exclusive of New York City, Buffalo, Rochester, Syracuse, and state institutions.

*Exclusive of New York City.

practical equivalent (grade special A raw) was extended to all cities or villages of 10,000 population or over. The cost of production of certified or special A raw milk has resulted in almost exclusive use of pasteurized milk in villages of this size. The estimate that at least 75 per cent of the population of the state are regularly supplied with pasteurized milk is probably an understatement. With these two major safeguards, water supply supervision and milk pasteurization in effect for a major proportion of the general population, it is not surprising that dysentery has been confined almost exclusively to small villages and rural areas or to temporary establishments, such as camps or summer resorts.

Table 7

EPIDEMICS OF DYSENTERY OF COMMON TYPES NEW YORK STATE,* 1932-1938

Year	Number of Epidemics			
	Flexner	Sonne	Others or Atypical	Total
1932	—	—	—	—
1933	2	—	1	3
1934	—	1	1	2
1935	1	1	—	2
1936	4	2	2	8
1937	4	7	1	12
1938	12	7	1	20
Total	23	18	6	47

Table 7 shows the place of occurrence of the outbreaks investigated during 1937 and 1938. It may be noted that the largest number of outbreaks and the largest number of individuals involved each year were associated with summer camps. A large number of the outbreaks occurred in state or private institutions. These were, with two exceptions, hospitals for the insane or feeble minded, which, because of the type of patient, present an unusual problem. A relatively small number of outbreaks occurred in the general population.

In each investigation an attempt was made to obtain sufficient epidemiologic data to identify the source of infection. The usual information concerning various water supplies, milk supplies and common sources of food used by each patient has been obtained. In apparent food-borne outbreaks information as to individual foods consumed has been obtained in an attempt to determine specific items in the diet responsible for the infection. As shown in Table 9, the epidemiologic investigations indicated that during 1937 and 1938 six epidemics were apparently due to the use of contaminated water supplies, two were due to contamination of milk, eight were believed to have been due to contact transmission, and in 13 conclusive evidence as to the method of transmission could not be obtained.

*Exclusive of New York City.

Table 8

OUTBREAKS OF BACILLARY DYSENTERY BY PLACE OF OCCURRENCE, NEW YORK STATE, EXCLUSIVE OF NEW YORK CITY, 1937 AND 1938

Place of Occurrence	No. Outbreaks		No. Cases	
	1937	1938	1937	1938
Camps	4	6	219	503
Summer hotels and boarding houses	—	1	—	13
State institutions	3	4	59	211
Private institutions	2	5	13	126
General population	3	4	61	165
Total	12	20	352	1018

Table 9

OUTBREAKS OF BACILLARY DYSENTERY BY METHOD OF TRANSMISSION, NEW YORK STATE, EXCLUSIVE OF NEW YORK CITY, 1937 AND 1938

Method of Transmission	No. Outbreaks		No. Cases	
	1937	1938	1937	1938
Water	2	4	104	394
Milk	—	2	—	166
Other food	—	3	—	146
Contact	4	4	123	39
Undetermined	6	7	125	273
Total	12	20	352	1018

A considerable proportion of the epidemics of dysentery as well as of other gastro-intestinal disease has occurred in summer camps and summer resorts which are in use for only two or three months during the year. Camps have been subjected to a certain amount of regulation and must obtain a permit from the local health officer. It has been obvious that supervision, especially of water supply systems, has been inadequate, due to the lack of a sufficient number of trained sanitary engineers to inspect and supervise the large number of these establishments. Summer hotels and boarding houses in the resort areas have received even less supervision. During the 1939

season, 12 additional engineers were employed and devoted full time to the inspection of camps, directing attention particularly to water supplies. Camps known to exist in the resort areas were visited and where inadequately protected water supplies were found improvements were made or emergency chlorination provided.

It is believed that considerable improvement was made, particularly in the water supplies used. Because of the large number of summer hotels and boarding houses and because of the lack of authority to enforce recommended improvements such as is provided in the instance of camps, relatively little improvement was made in the sanitation of resort hotels and boarding houses. Sanitary improvements in camps are believed to have resulted in a reduction in epidemic gastro-intestinal disease, especially of water-borne infection. Table 10 shows the reported epidemics of gastro-intestinal disease in camps and summer hotels during 1938 and the summer of 1939. It is interesting to note that there was a decrease in the total number of epidemics in camps in 1939 as compared with 1938, whereas there was an increase in the number of such outbreaks in summer hotels. The decrease in water-borne outbreaks in camps is particularly striking. Obviously other factors may have influenced the prevalence of gastro-intestinal disease in these establishments, but continued supervision of camps and extension of the supervision to other resort establishments seems indicated.

Table 10

EPIDEMICS OF TYPHOID FEVER, DYSENTERY, AND GASTRO-ENTERITIS IN CAMPS AND SUMMER HOTELS, 1938 AND 1939*

Mode of Transmission	1938				1939*			
	No. Epidemics		No. Cases		No. Epidemics		No. Cases	
	Camps	Hotels	Camps	Hotels	Camps	Hotels	Camps	Hotels
Water	13	5	512	84	4	14	173	607
Milk	1	0	105	0	0	0	0	0
Food	1	3	7	179	1	1	33	20
Others and undetermined	11	3	325	32	11	8	372	154
Total	26	11	949	295	16	23	588	781

*January 1 through October 1, 1939.

SUMMARY AND CONCLUSIONS

Bacillary dysentery is endemic in New York State and reported morbidity has increased markedly during recent years. This increase is believed to be due to more complete reporting rather than an actual increase in the disease. The prevalence of dysentery is significantly higher in small villages and in rural areas than in urban areas.

A large number of localized epidemics of diarrheal disease occur each year, especially in resort areas and in institutions. Prompt bacteriologic studies have shown a considerable proportion of these epidemics to be bacillary dysentery.

Inadequate protection of water supplies in summer camps and other resort establishments was found to be the cause of epidemics of dysentery as well as other gastro-intestinal disease.

Closer supervision of sanitation, particularly water supplies in summer camps, resulted in a decided decrease in epidemics of gastro-intestinal disease.

DISCUSSION (*Abstract*)

Dr. L. M. Graves, Memphis, Tenn.—Dr. Stebbins' studies have not only proven profitable in attacking an important problem in his own State, but they have developed procedures which are practical and urgent in every health district, rural or urban.

The degree to which typhoid fever has been suppressed in recent years is the pride of almost every health officer, and yet these studies bring sharply to our attention the somewhat embarrassing fact that in the case of dysentery we have not only fallen far short of solving the problem, but most of us have not even evaluated it. Dr. Stebbins' figures show that in New York in recent years both morbidity and mortality from bacillary dysentery far exceed the rates for typhoid fever. In looking over the rates for Memphis I find a similar situation here. Unless you have already done so, I am sure you will find it interesting to make this comparison in your own jurisdiction. And yet how many of us show the same concern over an outbreak of dysentery that we show over typhoid fever?

As was pointed out in Dr. Stebbins' paper, the problem of dysentery is more acute in rural than in urban areas. No area, however, is immune and the rates in any city are influenced by those of the surrounding territory. In the four-year period 1934-1937, a total of 174 deaths were recorded in Memphis. One hundred eight, or 62 per cent of these, were non-residents from the surrounding area who had been hospitalized in Memphis. It is not known how many of the other 66 received their infections outside the city. The age distribution here is similar to that in New York, but the seasonal occurrence is slightly earlier. Seventy-two

per cent of our deaths occurred in the four-month period, June to September, with the highest number in June.

Dr. Stebbins' observation that the increase in reported morbidity and mortality is due to better reporting rather than an actual increase in prevalence is undoubtedly true, and yet reporting is far from satisfactory. This may be due, in part at least, to the fact that we have not impressed the public with the importance of the disease and have not convinced the medical profession that we can and will do something about reported cases.

I was especially interested in Dr. Stebbins' connection of dysentery with summer camps and resorts. I am convinced that, so far as urban groups are concerned, these constitute one of our real dangers. Summer camps and camping for city young people have become very popular in recent years, and there are many camps catering to this trade. Stimulated by local residents who ask information relative to the safety of specific camps, the Memphis Health Department has, during the past season, made a survey of forty camps located in eleven different states. The survey was made possible through the cooperation of the health departments of the various states in which the camps were located. A summary of this survey indicates that approved sanitation has not kept pace with the rapid development of camps. Of the 40 camps surveyed, the following figures indicate the number in which important items of sanitation were considered satisfactory by the various state health departments:

Item Observed	Number Satisfactory	Per Cent Satisfactory
Water supply	31	77.5
Milk supply	17	42.5
Sewage disposal	32	80
Food handling	31	77.5
Swimming	35	27.5
Miscellaneous	37	92.5

It would seem from these figures that a system of control by the state departments of health, based on permits, similar to that carried out by Dr. Stebbins in New York, would be advisable in every state.

Dr. Archie L. Gray, Jackson, Miss.—In Mississippi there are reported approximately 9,000 cases of bacillary dysentery each year. It is very doubtful that we have as much bacillary dysentery as that. One physician in Mississippi found that approximately 35 per cent of all the diarrhea cases seen during a year were bacillary dysentery. In the last two or three years intensive study has been done in the laboratory in the State Board of Health on the problem of bacillary dysentery and an increasing number of specimens are being sent to the laboratory for that purpose. A very large percentage of those found positive are of the Flexner type with occasional Sonne.

We recognize that we have a great problem in Mississippi, but we do not feel that we have 9,000 cases a year.

Dr. Henry E. Meleney, Nashville, Tenn.—Dr. Stebbins had a large group of epidemics in which the source of infection was not determined. He did not mention excreta disposal in his camps. In the studies of bacillary dysentery in New Mexico by Hardy and his associates, it was found that the sanitation of a village with approved privies and with screening, I believe, reduced the incidence greatly. Of course, flies are a very difficult source to pin an epidemic upon, but I wonder whether he would comment on their possible importance, which seemed to be great in New Mexico.

Since Staphylococcus toxin in food is a frequent cause of acute diarrhea, I wonder whether Dr. Stebbins would tell us whether that source was excluded in his epidemics.

I should also like to ask what media were used for the isolation of the organisms and what method was used for collecting specimens.

Dr. James A. Crabtree, Washington, D. C.—In many parts of the country the terms "bacillary dysentery" and "epidemic diarrhea and dysentery" unfortunately are used very loosely by a large number of physicians. Oftentimes the diagnosis of specific bacillary dysentery is made on the basis of its epidemic occurrence rather than bacteriologic analysis. Consequently many cases which occur endemically fail to be entered into morbidity returns, while on the other hand many cases of diarrhea of nonspecific origin, when occurring during periods of high prevalence, are reported as specific bacillary dysentery.

In this connection I should like to ask Dr. Stebbins to give us the proportion of total cases reported in the State that were recorded during epidemics, as compared with the proportion recorded endemically as isolated cases. I should suspect the ratio of epidemic to endemic frequency to be quite large, and if so, one need hardly emphasize the great caution necessary in interpreting morbidity data from the point of view of either the present distribution or recent trends in incidence of the disease.

The discussion of Dr. Graves was of interest in emphasizing the administrative problems involved in an attempt to control a disease of this character in the average large municipality. The potential hazards arising from the use of summer camps and resort hotels, many of which are outside the range of influence of aggressive and effective public health supervision, emphasizes the regional character of the problem in that certain elements of it extend not only beyond the borders of municipalities, but also beyond those of individual states, and thus an effective solution of the problem calls not merely for individual health department action, but for a cooperative coordinated program set up on a regional basis.

Dr. Stebbins (closing).—In regard to Dr. McGinnes' suggestion that there may be an actually increased incidence of the disease, I doubt that this is true in New York State. There has been, of course, a marked increase in reported morbidity, but the case fatality rate has dropped consistently. There is probably an actual reduction in dysentery morbidity. Reporting is obviously very poor, but I think the general improvement in water supplies and in milk supplies must have had some effect on the incidence of the disease.

As to the sewage disposal in camps, there has been an attempt to make improvements. In previous surveys of camps, sewage disposal was found to be defective in a

large proportion and the reduction in the number of outbreaks in 1939 was probably not entirely due to improvement in water supplies. There has been a definite improvement in sewage disposal. There have been outbreaks that apparently were due to contact, and water supplies were in some instances polluted as a result of faulty sewage disposal. Improvement in sewage disposal certainly is an important phase of the control program. Emergency chlorination of water supplies can, however, be provided quickly and is a logical first line of defense.

I do not know what part flies have played in the transmission of infection in the outbreaks we have studied, but screening has been inadequate in many places. Staphylococcus toxin, that is pre-formed toxin, is believed to have been the cause of a considerable number of outbreaks.

The epidemics of food poisoning due to pre-formed toxin are distinctive clinically. The patients become ill soon after the ingestion of the responsible food and frequently within an hour or two of each other, and almost invariably following a common meal.

As to the collection of specimens, members of the department staff almost invariably make the investigation and try to get as many specimens from persons suffering from the disease as possible, preferably from the acute cases having active diarrhea at the time of the investigation.

We have classified these outbreaks as bacillary dysentery if any considerable number of cases have positive stools. That does not mean that each case had a positive stool, and in the examination of a large number of specimens we have occasionally discovered carriers of organisms other than the epidemic type.

I am sorry I cannot answer all the questions concerning the laboratory work. In New York State there has been developed a system of approved laboratories distributed throughout the State to which specimens may be sent. The specimens are collected by the field workers in 30 per cent glycerine and an attempt has been made to deliver them promptly either to the State Laboratory or to an approved local laboratory.

The technic in the approved laboratories may differ slightly, but must be approved by the Division of Laboratories and Research. As the bacteriologic procedures have been more closely supervised, a larger proportion of the specimens obtained have been found to be positive. One of our difficulties has been to obtain specimens early in the outbreak, and undoubtedly some of the failures to demonstrate organisms of the dysentery group have been due to delay in obtaining specimens. The primary object has been to identify the organism causing the outbreak. It has not been our purpose to obtain detailed information as to the efficiency of different bacteriologic procedures.

As to Dr. Crabtree's question in regard to the proportion of reported cases of dysentery occurring in epidemics, until quite recently epidemics of dysentery were recognized infrequently. In 1937 and 1938, epidemic dysentery formed by far the majority of recognized cases. There is, however, I believe, good reason to believe that an extremely small proportion of the non-epidemic cases are recognized and reported.

THE MAINTENANCE OF HEALTH AMONG RAILWAY EMPLOYEES*

By JAMES W. DAVIS, M.D., F.A.C.S.
Statesville, North Carolina

The prosperity of America and its security depend upon railway transportation. Anything affecting this transportation system vitally affects our nation.

Our great transportation captains of the past penetrated vast virgin domains, transformed them into almost inexhaustible granaries for feeding a craving world. They opened up to development mountainous fastnesses, from whose almost bottomless caverns have been evolved the fuel to operate our public utilities and other great enterprises, or the ore out of which have been fabricated our ships, our locomotives and all the vast machinery of industrial progress.

The trackless wastes are no longer trackless. Where the deep silence of centuries brooded, now are heard the myriad voices of world progress and the manifold sounds which constitute the melody of man's achievement.

With Aladdin-like magic, cities have risen where previously vast thickets afforded shelter for the denizens of the wilds, and art and science have grasped and utilized nature's potentialities and transformed them into utilitarian agencies that have made for the betterment and uplift of human society.

For these great achievements, for these miracle-like transformations, we are chiefly indebted to the keen vision and enterprise of railroad builders.

Our rapid national development and our far-flung commercial enterprises would have been impossible without the railroads. It is quite conceivable that without them our country would still have only the fringe of a civilization on our seacoasts and along our waterways, with nothing but wagon roads leading back into vast tracts of wilderness, to which no adequate transportation could bring any service. We should have been as Russia was up to 1910.

Whatever past quarrels the public may have had with the railroads, we want to look at the present and the future, facing the facts honestly. If we are interested in our own welfare, we must be interested in the railroads.

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*Chairman's Address, Section on Railway Surgery, Southern Medical Association, Thirty-Third Annual Meeting, Memphis, Tennessee, November 21-24, 1939.

Our present and future welfare depends on the railroads because we rely upon them to carry the bulk of the heavy freight of the country. Commerce and industry are kept going by their service. In spite of all that may be said about rates, railroad transportation is cheapest, safest, and best in the long run when all the costs are counted.

The railroads are involved in the heaviest single group of investments in the country. By these investments the country has greatly benefited, as well as by the services performed. The railroads are subjected to strict regulation and heavy taxation while they see their competitors, only lightly taxed, using the public highways which the railway taxation helps to maintain. They see the best of the business, the short hauls going to the other carriers.

One thing that can be done to help out the situation is the maintenance of health and efficiency among the vast army of railroad workers. Increased efficiency will result in better service, lower cost of operation and, at the same time, decrease the enormous cost of damages and repairs resulting from avoidable accidents.

The preservation of health among railroad employees is very important due to the fact that the lives of others depend upon these men having all their faculties working perfectly while operating trains, in any capacity whatever.

In the conservation of the health of railroad employees and in keeping up uniform efficiency among them, there are four major problems:

(1) The examination of all prospective employees.

(2) The periodic re-examination of all employees.

(3) The proper treatment of those who develop some disease requiring medical treatment.

(4) The cooperation of all employees in doing their part toward maintaining their health, strength and efficiency.

In the pre-employment examination, it is possible to eliminate a large majority of those unfitted for this type of work. This examination should be thorough and include, in addition to the physical examination, a fluoroscopic examination of the chest, Kahn or Wassermann test, urinalysis and any other special tests that may be indicated in any individual who is suspected of having some disqualifying condition or disease. If necessary, a stereoscopic x-ray of the chest, electrocardiogram and blood chemistry should be done. Certainly every test should be given to determine the fitness of the applicant for the work for which he is applying. Until this becomes universal, many individuals obtaining employment will become a burden rather than a help, a liability rather than an asset.

A great moral responsibility rests upon every examiner. When a man is found to be unfit for work, he should be carefully studied with a view to correcting the disabling condition present. If it is possible to correct the trouble, the man should be informed of this and the examiner should do everything possible to aid him so that, after treatment and relief of the disability, he may return for re-examination later and not be permanently disqualified. If this principle is not adhered to, we shall develop a class of unemployed and unemployables.

Some states have a department of rehabilitation to whom many of these individuals could apply for assistance and further advice, in case they are not able to obtain rehabilitation treatment otherwise.

A periodic re-examination should enable the company surgeon to detect any new conditions or diseases that have developed since the original examination. The periodic examination should be made at reasonable intervals. It is my opinion that a full-time examiner should do this when possible, and I believe that the pre-employment examination should also be done by a full-time examiner when this is practical. In this way, the examination is made by a man who has no other duties and who can take sufficient time to make each examination thoroughly and completely.

The problem of the treatment of those who develop a disease is great also. Any disease that an employee develops, which affects his safety as a worker or the safety of others, demands that he go off duty until he is able to resume his work satisfactorily and with safety to himself and others.

The treatment of those who develop an illness and the decision as to whether they are to remain on duty during treatment, or to return to work during treatment or after treament, is a great problem. In fact, it is sometimes a major problem.

It is not within the scope of my brief talk to discuss the various diseases but as an example it has been shown by a writer who has studied 35 definite syphilitic employees that these men lost 13,940 days from work. The cost of treatment

to their company was $25,296.10. The cost of lost time to their company was $25,415.00, making a total loss of $50,711.10. If 35 men could account for this much loss, I take it that an extensive and comprehensive survey of industry generally would show a staggering loss.

The problem of syphilis has been mentioned to show the effects of one disease. There are many other diseases and conditions which affect the employees of an organization adversely and cause a great deal of trouble, loss of time and expense to the company. In the solution of these problems, cooperation from everyone concerned is essential.

Education of employees to the fact that after their day's work is over they should conduct themselves so that they will be able and fit for the next day's work is another problem facing industry. While many employees no doubt feel that their time is their own after the day's work is done and indulge in various forms of amusement and dissipate freely without regard to their next day's work, yet they should be taught that this is wrong.

The pendulum which has swung to the left is now swinging back to the right and with it we shall see better cooperation among government, industry and employees, a situation necessary in order for our country again to be prosperous, for transportation to be made safer and the financial structure of our railroads more secure.

With the loyal cooperation of the railroad employees and with the financial backing (which, under existing conditions, should be extended to the fullest degree) of the great body of investors, there can be no question of a complete revival of the spirit of expansion and development which formerly dominated our vast railroad systems.

Transportation and civilization have been copartners in achievement. Each has been the correlative of the other. They have collaborated in writing the book of our destiny. The one has beaten down the barriers which, alone, the other could not surmount.

Keen appreciation of the fact that a country can grow and expand no faster than its railroads, that any deterioration in its transportation system means a proportionate strangling of its prosperity, and that neglect or oppression of the railroads means national retrogression, has slowly but surely pervaded the popular consciousness. The haze and mist which obscured our vision are gradually lifting. Today as never before we are justified in hoping that, with eyes to the front and the sordid past forgotten, business and transportation, guided and fostered by sane, unembittered legislation, may progress steadily onward and upward toward greater, more prosperous heights!

TRANSPLANTATION OF THE CORNEA*

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In recent years, corneal transplantation has created wide interest, first because of the fact that a tissue is transplanted from one individual to another; second, because a certain number of people have been made to see by this procedure who without it were doomed to permanent blindness; and third, because of the unusual difficulties which have been overcome in the development of successful keratoplasty.

The first attempt at substituting a transparent medium for the opaque cornea was made by de Quengsy in 1789. All of the eyes came to enucleation. From time to time others, notably von Walther, Mülbauer, Löhlein, Reisinger and Thomas, have transplanted clear cornea from the rabbit, monkey or other animal to the human being without success. These heterotransplants seemed to take and grow, but were invariably replaced by scar tissue.

Various methods of homotransplantation have appeared in the course of the development of keratoplasty. Lamellar keratoplasty, wherein only the external layers of the cornea were transplanted, was practiced by von Hippel, Fuchs, Löhlein and others. Some improvement in vision was obtained where the corneal scar was limited to the outer layers of the cornea. These grafts took well, but there was always scarring between the cornea of the host and the grafted cornea. Then, too, the scars were found often to involve all the layers of the cornea. Transplantation of the entire cornea was attempted by Wagenmann, Burke, Elschnig and Key. All of these transplants became opaque and in most of them glaucoma and phthisis bulbi ensued. Two other procedures are worthy of mention, namely, the corneal resection of Wiener in which a superficial scar was dissected off the cornea and epithe-

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lization allowed to take place and the autotransplantation of Morax in which there was an exchange of a clear peripheral portion of the cornea for the opaque center. Neither of these procedures gave appreciable improvement in vision.

The modern procedure is that of partial penetrating keratoplasty wherein a portion of the full thickness of the cornea is transplanted. The development of this type of keratoplasty has paralleled the other types, but it was not until Elschnig's report in 1930 that a significant series of favorable results was obtained. Later Filatov, Thomas and Castroviejo reported even better results. Elschnig used the von Hippel trephine to cut out the graft and held it in place by two sutures extending from limbus to limbus. Filatov inserted an ivory spatula through two keratome incisions behind the proposed site of the graft and cut down on it with a trephine. He held the graft in place by means of a conjunctival flap. Thomas made the initial incision with the trephine and finishing with the scissors obtained a bevel. Castroviejo made the initial incision with a twin-bladed knife, entered the anterior chamber with the keratome and completed the beveled incision with the scissors. Thus a square graft was obtained. Both Thomas and Castroviejo used a crossed suture in the cornea to hold the graft in place. Further improvements in technic may be confidently expected.

In the experimental work on rabbits at the University of Tennessee, I used the various technics of Elschnig, Filatov, Thomas and Castroviejo.

The technic of Castroviejo seemed to be the procedure best adapted to meet all the difficult situations that arise. Consequently, I have used this procedure in the twenty-one human cases which form the basis for this report.

INDICATIONS FOR TRANSPLANTATION

The indications for corneal transplantation depend upon the cause and extent of the damage to the eye, but in general it may be said that any case of corneal leukoma which seriously impairs vision calls for a corneal transplantation.

Corneal opacity is caused by many conditions. The most frequent of these are interstitial keratitis, ulcers, especially gonococcic ulcers, injuries, particularly burns, and corneal dystrophies. Unfortunately, there is often damage to the ocular structures beyond the cornea as a result of trauma or toxins associated with the cause of the opacity. The extent of this damage often cannot be determined with certainty before operation.

The most favorable cases for keratoplasty are those in which the corneal opacity is the only pathologic condition present in the eye. This implies that the cornea is not densely opaque throughout. Elschnig was the first to point out that the graft must be placed in apposition to an at least relatively clear cornea, that is, leukoma containing some corneal elements, if it is to remain clear. It seems that the graft is unable to obtain sufficient nutrition from scar to maintain its integrity as a transparent tissue.

Most cases which present themselves for transplantation exhibit a complicating disease. The unfavorable factors frequently encountered are trichiasis and entropion, dacryocystitis, symblepharon, corneal vascularization, both superficial and deep, dense scarring throughout the cornea, anterior and posterior synechiae, aphakia and glaucoma. Usually the retinal function can only be surmised by testing the light projection. It is obviously useless to operate upon an eye which has no light projection, but poor light projection does not necessarily contraindicate transplantation. Many cases must be operated upon in which the prospects seem very doubtful as a blind person is grateful even if he is enabled to see only large objects. In one instance a young boy had only one eye, badly damaged as a result of a burn. Light projection was poor. Transplantation resulted in only 1/200 vision, but he is one of my most grateful patients.

It is often possible to eliminate unfavorable factors before keratoplasty. To do this, multiple preliminary operations may be necessary. Trichiasis and entropion must be corrected. A chronically infected tear sac must be eliminated by dacryocystorhinostomy or extirpation. Symblepharon must be corrected by a plastic procedure to prevent vascularization of the graft, superficial blood vessels in the cornea must be removed by diathermy if they are few or it may be necessary to dissect off a whole mat of vascular tissue. If the cornea is densely opaque throughout, a preliminary transplantation may be done to supply corneal elements for the adequate nutrition of the final graft. A filtering operation must be done in the presence of glaucoma. Many cases present more than one unfavorable factor and require much persistence on the part of the patient and surgeon.

MATERIAL FOR TRANSPLANTATION

The material for transplantation is obtained from either of two sources, the enucleated eye or the eyes of the cadaver. The first source is limited almost entirely to eyes enucleated because of intra-ocular tumor. Eyes removed as a result of injury or glaucoma have rarely been acceptable. The second source of material is the eye removed from a cadaver within ten hours after death. The cadaver eye has proven to be as good as the eye enucleated from the living. Upon removal of the donor eye it is placed in normal saline until ready for use. It may be used immediately or kept in the refrigerator at 2° to 6° C. for as long as three days and still be in perfect condition for transplantation.

Contraindications to the use of an eye with a healthy cornea are few. Some surgeons have hesitated to use an eye affected with sarcoma of the choroid, but the eye enucleated for this cause is the chief source of material and no case of transfer of the tumor has been reported. The question of what general disease would contraindicate the use of an eye has not been settled. It is the consensus, however, that the eyes of untreated syphilitics should not be used. Blood compatibility has been found to have no significance. The age of the donor seems to be of little importance as grafts have been transplanted with equal success whether obtained from the six months old fetus or the old man.

One of the principle obstacles encountered has been the lack of a constant and dependable supply of corneas for transplantation. The supply of suitable eyes enucleated from the living is extremely limited and the eyes of cadavers are rarely obtainable in this country. In one instance, however, a man affected with progressing pulmonary tuberculosis willed his eyes for transplantation. Three grafts were obtained from the two eyes.

OPERATIVE TECHNIC

The operation that I have used follows, with a few minor modifications of my own, the technic of Castroviejo.

Instillations of pontocaine and retrobulbar injections of procaine are used for anesthesia, Akinesia is obtained by the O'Brien method. The lids are retracted by means of sutures in the skin near the margins and the globe is immobilized by superior and inferior rectus bridle sutures. A section 4-5 mm. is outlined in the cornea with a twin-bladed knife. Sutures of fine corneal silk are placed into the cornea approximately 1 mm. from the section all around producing a Maltese cross effect. To accomplish this, the needle is inserted into the superficial layers and, traversing 2.5 mm. of cornea, is brought out at the upper right cornea; inserted at the lower left corner and brought out at the middle of the lower side; inserted at the middle of the upper side and brought out at the upper left corner; inserted at the lower right corner and brought out at the middle of the right side; inserted at the middle of the left side and brought out 2.5 mm. beyond. This single suture is left in large loops and smoothed out of the way during the section. A traction suture is placed in the square section. Fluorescein is instilled better to outline the section. A keratome incision is made at the upper side of the square at an angle of 20 degrees; the remainder of the square is cut out with special scissors while traction is exerted with the suture previously inserted. The beveling of the margins to 20° is sufficient to prevent the graft from falling into the anterior chamber.

The recipient eye having been prepared, the donor eye is wrapped in gauze, the cornea remaining exposed, and the graft is cut out in exactly the same manner as the segment from the recipient eye, except that no traction suture is used. The graft is then transferred to the recipient eye, fitted snugly into the defect and the suture drawn taut and tied. The crossed suture and beveling insure maintenance of the position of the graft.

POSTOPERATIVE COURSE

During the first few days the graft imbibes aqueous and becomes somewhat cloudy. Soon the endothelium and epithelium grow over the bridge of fibrin between the graft and the host. The graft becomes clear between the fourth and eighth day and remains so. This is the sequence of events if the apposition of the wound edges is accurate and the condition of the cornea of the host is good. If conditions are less favorable the edema may last longer before clearing occurs and a secondary clouding may occur during the third week. This later clouding produces a varying degree of permanent nebulosity of the graft. If the condition of the cornea of the host is poor, whether the apposition is good or not, the initial edema passes over into infiltration and vascularization of the graft leaving a permanent opacity.

RESULTS

The results of the twenty-one keratoplasties which form the basis for this report are briefly summarized in the accompanying tables.

Table 1 is a classification of the condition of the graft after healing has been completed. An ultimate opacity equal to or greater than the original leukoma is considered an unsuccessful transplantation. Any degree of resulting transparency may be expected to give a corresponding improvement in vision, other factors being equal, and is considered a successful transplantation. The visual outcome, however, does not always parallel the transparency of the graft because of pathologic changes behind the cornea.

Table 1

CONDITION OF GRAFTS AT LAST OBSERVATION

Graft transparent as normal cornea	4
Graft slightly less transparent than normal cornea	5
Graft nebulous	5
Graft more transparent than original leukoma	1
Graft opaque as original leukoma	4
Graft densely scarred	1
Graft lost	1
Total	21

Visual results are summarized in *Table 2*. When vision of 6/60 or better is obtained the result is considered good. Improvement was noted in five cases. Vision in these was respectively 1/200, 2/200, 2/60, 4/60 and 6/120. In those classified as worse, vision was reduced from moving objects to light perception. One graft was lost from infection. In order to evaluate the visual results fairly, one must take into consideration the pathologic conditions present in the eye receiving the transplant. The leukomatous eyes are classified into two groups, according to whether they are favorable or unfavorable for keratoplasty. In the favorable eye, the leukoma is not so dense that no corneal elements are present, the anterior chamber is fairly normal, light projection is good and the tension is normal. If only favorable eyes were selected for keratoplasty, the outcome would be successful in a far larger number of cases. In this group of cases fourteen of the twenty-one eyes were regarded as unfavorable. *Table 3* presents a comparison of the visual results in the favorable and unfavorable cases. The case is considered successful if the vision is appreciably improved.

Table 2

VISUAL RESULTS

6/60 or better	8
Improved	5
Unimproved	5
Worse	3
Total	21

Table 3

VISUAL RESULTS IN FAVORABLE AND UNFAVORABLE CASES

Favorable cases	7	Successes	86 per cent
Unfavorable cases	14	Successes	57 per cent

SUMMARY AND CONCLUSIONS

It has been the purpose of this paper to review the subject of corneal transplantation. The development of keratoplasty, indications and source of material for transplantation are briefly discussed. The operation used by the author is presented together with the postoperative course and results obtained in 21 cases.

The advent of successful keratoplasty has brought an important addition to the established methods for restoring vision. It has its application in a group of cases which heretofore carried a hopeless prognosis.

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SULFAPYRIDINE IN PNEUMONIA*

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This report relates to the use of sulfapyridine in the treatment of twenty-six consecutive adult cases of pneumonia admitted to the Medical Service of the Clinic-Hospital of San Angelo between January 15, 1939, and August 15, 1939. Although reports on this subject are numerous and concordantly favorable in indicating therapeutic effectiveness of sulfapyridine in the pneumococcus pneumonias, far too little attention has been paid to the limitations and untoward effects of this chemotherapeutic agent, a subject emphasized by this study.

Actually thirty-two cases of adult pneumonia were treated on this service during this period; efforts to establish an unequivocal bacteriologic diagnosis failed in six cases in which there were no mortalities. These efforts included careful study of "lung" sputum, lung suction culture often with mouse peritoneum transfer, and admission blood culture. In addition, each patient had a confirmatory chest x-ray and complete blood count, urinalysis, carbon dioxide combining power determination, and, in patients over 50 years of age, a blood urea nitrogen determination. Subsequent daily blood counts, urinalyses including urine urobilinogen determinations, and determinations of free blood sulfapyridine by the Marshal-Litchfield method were done in every case.

Twelve of the twenty-six patients were more than 50 years of age. And very unusual is the relatively high incidence of Type XIV infection, of which there were five cases in twenty-one pneumococcic pneumonias, two with bacteremia. Six of the twenty-one pneumococcic pneumonias were bacteremic, one Type I, one Type XVIII, one Type V, one Type VII, in addition to the above. Remaining bacteriologic diagnoses included one typhoid, one tuberculous, one primary *Staphylococcus aureus*, and two non-hemolytic streptococcic pneumonias.

The dosage schedule employed consisted of the administration of two grams of sulfapyridine as the initial dose and one gram every four hours thereafter until a total of twenty-five grams had been given or until gastric intolerance or contraindications prohibited further use of the drug. Beginning April 10, 1939, this schedule was altered in that four grams of sulfapyridine was administered as the initial dose and one gram every four hours thereafter until the temperature had fallen to 100° or less; then one gram three times daily until physical signs manifested resolution or contraindications arose. In instances of gastric intolerance, four grams of sulfapyridine in 1,000 c. c. of dextrose-saline was administered by drop venoclysis daily. In addition to sulfapyridine, patients received physiologic supportive care, with oxygen and other medication as indications warranted. Specific rabbit serum was administered in two cases, in which the fever did not decline at the expected time in spite of what is considered adequate free blood sulfapyridine concentration.

Study of the free blood sulfapyridine concentrations in this series fails to demonstrate any relationship between the level of free drug in the blood and the ratio of dosage to body weight. One of two patients of approximately the same age and weight on the same dose schedule developed a free blood sulfapyridine concentration of only 1.6 mg. per cent; the other attained a level of 13.3 mg. per cent. Further, no optimal blood level for free sulfapyridine is indicated in this material. Patients with comparable severity of illness did equally well apparently on concentrations varying from 3.5 to 13.3 mg. per cent. On the dose schedules employed only one patient failed to attain a concentration of at least 3.5 mg. per cent. The incidence of toxic effects in this series cannot be shown to be directly related to the free blood sulfapyridine level; no toxic reactions were encountered in cases with free drug concentrations above 10 mg. per cent, but, paradoxically, a fatal toxic reaction occurred in a case which attained a level of only 1.6 mg. per cent. These observations cause one to question the importance of studies of the blood sulfapyridine level.

The results obtained in these cases are as favorable as those reported by others.[1-6] Although three mortalities occurred in this series of twen-

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ty-one pneumococcus pneumonias, none can be attributed to pneumonia or to sulfapyridine failure directly. Two deaths were the direct result of sulfapyridine toxicity. The third, a 38-year-old male, expired suddenly on the fifteenth day of illness after recovery from pneumonia was established. Autopsy demonstrated massive pulmonary embolism of the unaffected lung. The source of the embolus was not demonstrated. Sixteen of twenty-one pneumococcus pneumonias responded to sulfapyridine with precipitous defervescence to 100 degrees or less within 24 hours. Characteristically, however, this improvement was reflected in neither the appearance of the patient, his subjective symptoms nor by the pulmonary physical signs. Three pneumococcus pneumonias failed to respond to sulfapyridine alone. They will be discussed below. A primary *Staphylococcus aureus* lobar pneumonia manifested no defervescence after 7 days of sulfapyridine, but recovered rapidly with spontaneous copious postural drainage. An atypical typhoid pneumonia and a tuberculous lobar pneumonia continued with unabated fever on sulfapyridine therapy, refuting the contention that the drug has an antipyretic action. A Type III non-bacteremic lobar pneumonia in a 73-year-old man failed to respond to sulfanilamide (16 mg. per cent blood sulfanilamide) and spread on the sixth day to the opposite lung. It responded immediately on the eighth day to sulfapyridine, and the patient recovered. The duration of the disease and the number of hospital days appeared shortened only in the few cases seen early.

Toxic effects ascribed to sulfanilamide are to be anticipated with sulfapyridine, particularly in the hematopoietic system. Hemolytic anemia, which usually appears within the first five days of chemotherapy, was not detected by urine urobilinogen studies. Granulocytopenia, seen mainly after prolonged or intermittent chemotherapy, was not encountered, the decline in the neutrophilic elements being commensurate with the improvement in each instance. Drug fever, which is expected to occur on the tenth day of the first period of treatment and the second day of the second period, was not seen. Cyanosis, unlike our experience with sulfanilamide, was rarely noted and slight at most. Gastro-intestinal symptoms are peculiar to sulfapyridine in their frequency. Anorexia occurred in all cases after a few hours of chemotherapy; nausea was complained of by half of the patients, and vomiting prohibiting oral administration occurred in six instances. Patients who received oxygen presented these symptoms with striking infrequency; they were, of course, more seriously ill and, by and large, a more contented group. Hepatitis was not observed. Neither was neuritis recognized to occur in this group, although mild mental aberrations of a depressive type were common, and in two instances were of such severity as to constitute definite psychoses of a peculiar type,[5 7] directly contributing to mortality in one instance.

A 66-year-old retired railroad superintendent, with an alcoholic history and recent alcoholism, was admitted March 21, 1939, with right upper lobar pneumonia, Type XIV pneumococcus, bacteremic. Blood count revealed 6,900 leukocytes. His pulse was 134, temperature 100.4°, respirations were 22 and shallow. Five hours after the initial dose of sulfapyridine he appeared groggy and talked incoherently. His condition progressed in the next six hours to an uncontrollable peculiar delirium in which he was constantly moving, the movements being waxy and deliberate but without purpose, and he was uncooperative. He expired on the third day from peripheral circulatory failure precipitated by uncontrollable delirium.

The renal effects of sulfapyridine manifested as hematuria, ureteral colic and azotemia have received emphasis in the recent literature in which a number of deaths have been attributed to this effect[3 5 8 9 10] and demonstrated to result from ureteral obstruction and renal irritation by acetyl sulfapyridine calculi.[11 12] A fatality of this origin occurred in this group.

A 71-year-old retired ranchman was admitted on March 9, 1939, with a right lower atypical pneumonia, sputum pneumococcus Type XXXI, lung suction culture Type XIV, non-bacteremic. Blood count revealed 12,850 leukocytes, temperature 101°, pulse 110, respiration 28, blood pressure 240/120, blood urea nitrogen 25 mg. per cent, and carbon dioxide combining power 56 volumes per cent. On the fourth day of sulfapyridine he developed gross hematuria, whereupon the drug was omitted. The condition progressed to oliguria, severe ureteral colic, stupor, anuria, coma, and the patient expired on the twelfth day in uremia and acidosis with blood urea nitrogen 88 mg. per cent and carbon dioxide combining power 34 volumes per cent. Relevant postmortem findings were: contracted granular kidneys (old vascular nephritis), moderately dilated renal pelves and ureters, especially on the right, pelvic mucosa congested, pelves filled with dark brown fluid (embalmed) containing gritty material.

Previous kidney damage is no requisite for the occurrence of this effect of sulfapyridine. Although previous reports indicated infrequency of this complication in children, the report of Tsao, *et al.*[10] suggests no age immunity; according to these authors, the reaction of the urine is no determiner, although Long and Wood[5] advocate prophylactic alkalinization of the urine

(pH 7.5) to hinder acetyl sulfapyridine precipitation.

Failure to respond to sulfapyridine should be carefully analyzed in each instance in order that the limitations of the drug may be recognized and the place of chemotherapy in pneumonias be definitely and expediently established. The sulfapyridine used may be an inactive preparation. Theoretically this may be due to attachment of the pyridine radical to the sulfanilamide radical in some other position.[13] The species of pneumococcus may be innately resistant to sulfapyridine,[14] or may develop tolerance to the drug.[15] It is possible to mistake the etiologic organism, particularly in the higher type pneumococci when only the sputum is studied. The drug may be insufficiently absorbed from the gastro-intestinal tract, or after adequate absorption, it may be excessively acetylated. Although one of the above may occasionally prove to be the mechanism of sulfapyridine failure, in the main and from the aspect of clinical practicability, failure of sulfapyridine response is not synonymous with sulfapyridine failure.

A Type I lobar pneumonia and a Type XIV lobar pneumonia, both bacteremic, critically ill and seen late, failed to respond with defervescence after 48 hours of chemotherapy. Both responded dramatically upon the addition of specific rabbit serum.

A Type V lobar pneumonia with bacteremia and massive empyema failed to manifest any defervescence on five days of sulfapyridine, but responded with fever decline to normal within 24 hours following institution of surgical drainage.

Failure to respond to sulfapyridine can mean failure to recognize an impaired immunity mechanism, and the need for antibodies or drainage of a focus. At the risk of over-simplification, ultimate recovery in pneumonia can be said to depend upon the phagocytosis of causative bacteria by body leukocytes. Before this can be done, however, the bacteria must be killed and their specific carbohydrate substances neutralized by specific antibodies. It would appear that the action of sulfapyridine is limited to a bactericidal one independent of the immunity mechanism; but the immunity processes must provide the specific antibodies necessary for recovery. An impairment of the immunity mechanism may be anticipated in overwhelmed bacteremic cases seen late and in complicating empyemata to and in which antibodies are attracted and bound. Pneumonia in pregnancy, and in the aged, should be added to this category, as well as Type III pneumococcus infections for reason of the poor antigenicity of the Type III pneumococcus.[16]

SUMMARY

Our experiences with sulfapyridine in the treatment of the pneumococcic pneumonias have given results concordant with those reported by others, and substantiating the belief that sulfapyridine is of great value. That chemotherapy has simplified the management of the pneumonias, and that sulfapyridine has supplanted previously established methods of treatment, is denied by these observations. Intelligent treatment of the pneumonias will continue to require bacteriologic search for the cause, physiologically sound supportive care, recognition of and expedient treatment for anoxemia, peripheral circulatory failure, pulmonary edema and impaired immunity mechanism. Additionally now, chemotherapy requires close scrutiny for toxic drug effects necessitating daily blood counts and urinalyses. Daily determination of the blood sulfapyridine as extolled in some quarters appears to be neither necessary nor practicable.

CONCLUSION

Cognizant of its limitations and toxic effects, we have in sulfapyridine a valuable addition to our armamentarium for the management of the pneumococcic pneumonias.*

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TOXIC EFFECTS OF SULFANILAMIDE*

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Three years ago at the annual meeting of the Southern Medical Association in Baltimore, we listened with rapt interest when Long and Bliss reported their original investigation on "Experimental and Clinical Observations Concerning Prontosil, Prontosil S, and Para Amino Benzene Sulfanilamide." This study stimulated the medical profession of America to further investigation of sulfanilamide and its related compounds.

Our own interest originally was in connection with sulfanilamide in the treatment of infectious diseases. Hesitant at first on account of the potential toxic action which might result from overdosage, this fear has been dissipated to a large extent through clinical experiences and blood studies over a period of three years.

There remains little doubt that many side effects of sulfanilamide do occur and at the same time relatively few deaths have been attributed to its use.

The out-patient department of the John Gaston Hospital in Memphis, Tennessee, has a monthly average attendance of 15,000 ambulatory patients. Concerning this large number of patients we were anxious to secure certain information:

(1) The total amount of sulfanilamide dispensed during the course of one month or during the course of the year.

(2) How much sulfanilamide is prescribed for each patient in the departments using the largest quantity?

(3) What instructions are given clinical patients as to possible toxic complications?

(4) What efforts were being made to check hemoglobin or total white counts on patients receiving sulfanilamide or its derivatives?

In answer to our first question:

Forty thousand five-grain sulfanilamide tablets are dispensed monthly at the out-patient department of the John Gaston Hospital. This is exclusive of ten thousand five-grain tablets prescribed monthly for patients in the John Gaston Hospital. The total for the year is 480,000 five-grain tablets, or 2,400,000 grains. Added to this, 600,000 grains from the John Gaston Hospital totals 3,000,000 grains, or 375 pounds. The pharmacist in charge of the drug department claims that one sulfanilamide tablet is dispensed for each tablet of acetyl salicylic acid dispensed.

What was the average amount of sulfanilamide dispensed to each patient in the department using the largest quantity?

The urologic department dispenses 20,000 five-grain tablets monthly, the gynecologic department 10,000 tablets, and all other departments total 10,000 tablets.

The average dosage prescribed in the genito-urinary department is as follows:

80 grains daily for 3 days	240 grains
60 grains daily for 3 days	180 grains
40 grains daily for 10-14 days	450 grains
Total	870 grains

Sodium bicarbonate is frequently prescribed with sulfanilamide to prevent acidosis.

The above dosage may be repeated three or four times on expiration of the amount given. Therefore, it is not unusual for patients to receive a total of 1,500 to 3,000 grains before discontinuing the drug.

What instructions were given clinic patients as to possible toxic complications?

The majority are instructed that severe headache, vomiting, weakness, chills, fever, or jaundice, are indications for cessation of the drug and that they should report these symptoms to their physician. If the toxic effects justify hospitalization, this is done immediately.

What efforts are being made to check hemoglobin or total white counts on patients receiving sulfanilamide or its derivatives?

Obviously it would be extremely difficult to check with blood counts each patient receiving

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sulfanilamide in the out-patient department of a large hospital. Therefore, only the occasional patient has the benefit of adequate blood studies. It is felt that this is a very important question and some effort should be directed toward its correction.

We next decided to gather further information from our colleagues in the Memphis and Shelby County Medical Society and a questionnaire was submitted to 175 members. Sixty-six replies were received.

The first question asked was as follows:

Approximately how many patients have you treated with sulfanilamide, "neoprontosil" and sulfapyridine from 1937 to date?

The total number of patients treated with sulfanilamide by 57 physicians was 6,522; the average number per physician was 114.

The total number of patients receiving "neoprontosil" was 4,311, prescribed by 50 physicians. The average number treated was 86 patients.

The total number of patients receiving sulfapyridine was 371 prescribed by 22 physicians. The average number treated was 17 patients. Certainly this bespeaks the intensive use of these new chemotherapeutic agents.

The second part of this inquiry contained a list of twenty-four complications and requested a check of these complications in the order in which they have occurred in the physician's practice and the number of times.

The tabulation compiled below records the complications and the check number corresponds to the number of physicians reporting these complications:

Nausea	50	Diarrhea	15
Cyanosis	49	Heliosensitivity	10
Lassitude or weakness	45	Hemolytic anemia	8
Malaise	42	Paresthesia	8
Vomiting	41	Difficult micturition	7
Depression	39	Dermatitis	7
Anorexia	38	Jaundice	7
Headache	36	Lowering of carbon dioxide combining power	6
Vertigo	35		
Mental confusion	33		
Inability to concentrate	28	Morbilliform eruption	7
Fever	26	Hepatitis	6
Abdominal pain	21	Constipation	4
Dyspnea	20	Pruritus	4
Tinnitus	19	Purpura eruption	3
Scarlatiniform eruption	19	Granulocytopenia	3
Urticarial eruption	15	Optic neuritis	1

Certain of these complications deserve separate comment.

CYANOSIS

Cyanosis of varying degrees frequently developed in the practice of 48 physicians prescribing sulfanilamide therapy. The time of its appearance was usually during the first or second day.

The mechanism of the production of cyanosis is not clear and has been attributed to the formation of sulfhemoglobin, methemoglobin, to an unknown cause, possibly a discoloration of the red blood cells by a pigment formed in the course of sulfanilamide therapy, or to reduced hemoglobin.

The cyanosis varies from a mild bluing of the nail beds or lips to a slaty discoloration of the entire body. In a majority of cases cyanosis may be disregarded. With each prescription of the drug, we believe it advisable to mention the possibility of an ensuing discoloration of the skin. Recovery is prompt on withdrawal of the drug or following the use of methylene blue intravenously. The dosage as recommended by Wendel is 0.1 to 0.2 c. c. per kilogram of body weight of a 1 per cent aqueous solution intravenously. The dye should be injected slowly and carefully.

Sulfates should be forbidden during the administration of sulfanilamide because of the possible danger of precipitating sulfhemoglobinemia.

NERVOUS SYSTEM

The majority of complications, as tabulated by question two, were toxic manifestations referable to the nervous system, namely: nausea, lassitude or weakness, headache, vomiting, depression, anorexia, vertigo, mental confusion, inability to concentrate, fever, and abdominal pain.

The nausea, anorexia, malaise and vomiting as frequent complaints are probably due to a central action of the drug and not to its local irritating effect.

Headache is often encountered. This symptom frequently passes off quickly, but it must not be overlooked as a possible danger signal of dermatitis, acute hemolytic anemia, and drug fever.

Depression has been noted in a few cases, especially where large initial dosage has been instituted. Two of our patients appeared greatly depressed and disoriented.

Central or peripheral neuritis is a rare complication. Stanford, in a personal communication,

mentioned a case of optic neuritis attributed to sulfanilamide with uneventful recovery. Etter reports a case with severe convulsions two hours following each dose of sulfanilamide on three successive occasions.

Skin.—Judging from replies, skin manifestations are quite numerous. Scarlatiniform, urticarial, heliosensitivity, morbilliform, and purpuric eruptions have appeared in the order named. These skin rashes usually occur on the seventh to tenth day of treatment and disappear twenty-four to thirty-six hours after discontinuance of the drug.

Blood Disturbances.—In our series of five hundred cases treated at the Isolation Hospital, where relatively large dosage is employed, we have come to the conclusion that it is exceptional for sulfanilamide to produce a direct effect upon the white cells. It must be appreciated that the slight depression of the leukocytes is temporary and that as soon as the infection is brought under control the white count returns to normal.

Granulocytopenia has occurred in only one case which came under our observation. This complication appeared one to two weeks following administration of the drug.

The following case briefly recites the course of events in a patient who developed agranulocytosis following sulfanilamide treatment for streptococcus sore throat:

Agranulocytosis.—M. N., a white man 25 years of age, a chronic alcoholic, developed a sore throat following one of his weekly "drunks." His private physician prescribed twenty grains of sulfanilamide every four hours for six doses. After the sulfanilamide he was very cyanotic, nauseated and was unable to retain any food or water. He complained of cramping abdominal pains, pain in his legs and marked generalized weakness. Four days later (August 26, 1939) on admission to Isolation Hospital, his temperature was 98.6°, pulse 112, respiration 24, blood pressure 65/300. The cyanosis was extreme and he appeared very weak. Stimulants were given immediately. Methylene blue 10 c. c. was given intravenously, likewise gluco e in saline, and gastric lavages. The blood count was 12,400 white blood cells, 72 per cent polymorphonuclears and 21 per cent lymphocytes. The red blood cells were 4,930,000, hemoglobin was 15.3 grams, and the methemoglobin on admission was 1.8 per cent (Wendel). The urine was negative. Two days after admission 10 grains of "neoprontosil" were given orally. On the third day 15 grains of sulfanilamide were given orally before he was discharged greatly improved. Six days after discharge he was seen as an outpatient. He complained of cramping in his feet, tingling and numbness, weakness of all extremities and inability to coordinate his muscles. On account of these symptoms he was readmitted to the John Gaston Hospital on September 26, 1939. This was eight days after his discharge from the Isolation Hospital. His temperature was 100°, pulse 140, respiration 23, and blood pressure 112/59. Blood findings were: red cells 3,590,000, hemoglobin 11 grams, white blood cells 2,100, lymphocytes 58 per cent, polymorphonuclears 34 per cent. The next day his red blood cells were 2,522,000, white cells 1,450, hemoglobin 9.8 grams, 80 per cent lymphocytes, nonfilamented 4 per cent, filamented 16 per cent, blood culture negative, and spinal fluid negative. On this day, October 8, his temperature was 102°, pulse 130, respiration rate 140, and reflexes were absent. He could not evert his feet, was unable to flex his knees, had lost his position sense, blood culture was negative. Complained of sharp dyspnea, nausea and vomiting. He became delirious. X-ray of his chest was negative. He had to be restrained in bed. There was an eruption over his trunk. His pulse was very weak. Treatment during his second admission consisted of sodium phenobarbital, a transfusion of 500 c. c. of citrated blood, pentnuleotide, caffeine sodium benzoate, 1,000 c. c. of glucose intravenously, crystalline vitamin B_1 intravenously, and an oxygen tent. His condition grew steadily worse, pneumonia developed and the patient expired two days after development of the agranulocytosis and sixteen days after beginning the sulfanilamide treatment.

Autopsy revealed a large gastric ulcer and pneumonia. No bone marrow studies were done.

Mild hemolytic anemia may occur in many individuals. This has been true in our cases where therapy has continued for two or more weeks. There may occur a sharp decrease in the red blood cells with a corresponding decrease in the hemoglobin content.

Acute hemolytic anemia usually occurs three to seven days after treatment has started. This condition is characterized by sudden onset with a marked decrease in the red cells and hemoglobin, jaundice, marked reticulocytosis and leukocytosis. One death has occurred in our series.

FATAL HEMOLYTIC ANEMIA

C. H., a negro man, aged 23, was admitted to the Isolation Hospital on my service May 21, 1938, with gonorrheal conjunctivitis involving the right eye. Swelling, edema, redness and discharge from the eye were of five days' duration prior to hospital admission. Gonorrheal urethritis was of three weeks' duration.

The patient was a well developed and apparently well nourished man. No icterus or pallor were present. Except for the eye and urethral discharge, no physical abnormalities were noted.

The oral administration of sulfanilamide was begun on May 21, when a total of 140 grains were administered. Further amounts given were May 22, 120 grains; May 23, 120 grains; May 24, 80 grains; and May 25, 60 grains, a total of 520 grains.

Urinalysis of a non catheterized specimen on May 23 showed 20 pus cells per high power field.

The blood Kahn on the same day was negative.

The right eye smear on May 21 was positive for gonococcus.

BLOOD CELL EXAMINATIONS

	May 23	May 24	May 26	May 27	May 30
Red blood count	3,550,000	3,600,000	1,650,000	2,650,000	2,850,000
White blood count	6,400	9,700	19,200	28,600	16,400
Hemoglobin, grams	13	13	7.5	7.5	7.5
Polymorphonuclears, per cent	71	—	84	—	—
Lymphocytes, per cent	27	—	16	—	—
Eosinophils, per cent	2	—	—	—	—
Blood platelets	Normal				

Four days after admission, May 24, the patient refused medication and complained of nausea and abdominal pain.

On May 26, continued nausea and abdominal pain were noted, with hiccoughs and frequent eructation of gas. The abdomen was very rigid. Jaundice was generalized.

There was suppression of urine. Methylene blue, 10 c. c. intravenously, was given.

On May 27, hiccough and vomiting continued. He was given 500 c. c. of citrated blood.

On May 28, the icteric index and Vanderberg test showed hemolysis. Nausea, vomiting, abdominal pain and jaundice were of three days' duration. There was generalized abdominal tenderness. Nonprotein nitrogen was 222 milligrams per 100 c. c. of blood. Methemoglobin was 8 per cent, sulphemoglobin 8 per cent, and blood chlorides 490 milligrams per 100 c. c. of blood.

Urinalysis of a catheterized bladder specimen on May 29 showed: Amount, only one ounce obtained; color, smoky; reaction, acid; albumin, 3 plus; acetone, negative; bilirubin, negative; and occult blood, 4 plus.

The patient was irrational and respiration was labored and loud. There was epistaxis.

On May 30, his skin was cold and clammy, he was dribbling mucus from the mouth, and there were noisy respiratory efforts.

On May 31, the blood nonprotein nitrogen was 286 milligrams per 100 c. c. of blood, and blood chlorides were 520 milligrams per 100 c. c. of blood.

The patient expired May 31, 1938. Necropsy was refused.

The treatment, in addition to blood transfusion, consisted of frequent stimulations, with caffeine, sodium benzoate and multiple infusions of hypertonic glucose solution.

The third question asked was: "Do you routinely carry out blood studies before and after the use of sulfanilamide or its compounds?"

Thirteen physicians routinely carried out this procedure. One replied, "After sulfapyridine but not after sulfanilamide and 'neoprontosil'." Six replied that routine blood counts were uniformly done on hospital patients. One pediatrist replied that it was routine in his practice to check bloods before and after treatment and then one month later.

The routine daily blood count of a recent erysipelas case at Isolation Hospital who received a total of 170 grains of sulfanilamide in three days showed a sudden drop of leukocytes from 4300 to 2800. Stopping the drug and one blood transfusion quickly brought the count back up to normal limits.

We have encouraged our students at all times routinely to check hemoglobin and total white cell counts of all patients receiving sulfanilamide or its related compounds.

Our final question was concerned with the number of deaths following the use of sulfanilamide or any of the allied compounds.

Stephenson, two years ago, reported a death following "elixir of sulfanilamide" poisoning. Two other deaths were mentioned earlier in this presentation.

SUMMARY

From this study mild toxic symptoms such as headache, nausea, lassitude or weakness, malaise, anorexia, vertigo, and mild cyanosis may be easily identified and controlled. These symptoms should not cause concern.

Marked dyspnea, sharp cyanosis, severe abdominal pain, depression, mental confusion, diarrhea, fever, skin eruption, slowly developing anemia, and lowering of carbon dioxide tension, are dangerous manifestations and must be treated with respect. Dosage should be reduced immediately or the drug discontinued.

Acute hemolytic anemia, neutropenia, jaundice, optic neuritis, demand immediate discontinuance of the drug. Daily examination of the blood is imperative and emergency measures such as forcing of fluids, blood transfusions, oxygen and intramuscular pentnucleotide injections. Intravenous methylene blue to combat methemoglobinemia is of much value.

COMMON ERRORS IN THE DIAGNOSIS AND TREATMENT OF THE ANEMIAS*

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In this age of rapid advancement in medical knowledge, the great cry had been for something new. Physicians are so alert for newer and better methods of treatment that I fear we often forget older, well-proven facts. This results in quite a breach between scientific knowledge and the practical application of this knowledge in our practice of medicine. It is this gap which I wish to discuss in the general treatment of the anemias.

Anemia is too often considered and treated as a disease rather than a symptom. In the newer, and no doubt better, classification of macrocytic and microcytic anemias, we have lost the practical reminder of the older classes of primary and secondary. The large majority of cases of anemia are truly secondary to a cause which should be found. Lest I be accused of living in a glass house, before casting any stones, I will present a brief case abstract to illustrate this common mistake made by my own hasty conclusion.

Case 1.—In September, 1933, S. W., a seventeen-year old white boy, was seen with the complaints of fatigue, headaches, and spots before the eyes of three weeks' duration. He also complained of a seasonal hay fever with several nosebleeds during the preceding two weeks. The history was otherwise essentially negative except for occasional "gas pains" in the abdomen to which he attached little significance. Physical examination was entirely negative except that the boy was underweight and appeared pale. A blood count revealed a moderate microcytic anemia. With the typical symptoms of anemia, I concluded that the nosebleeds were the probable cause, advised pollen tests for the hay fever, prescribed iron and a high caloric diet.

The patient did not report again until June, 1935 (twenty months later). At this time he stated the fatigue and headaches had improved definitely after taking the iron only to return later, when he would get the prescription refilled. A more careful systemic history revealed that there had been four or five attacks of epigastric distress in the previous two years. These occurred particularly in the spring and fall, lasting on the average of two weeks to two months. The distress was of a burning character, worse when he was tired, relieved by soda, food, milk or rest. There was no history of tarry stools. Physical examination now revealed a small area of abdominal tenderness just to the right of the umbilicus. Stool examinations while the patient was on a meat-free diet showed a positive benzidine test. Stomach fluoroscopy revealed a duodenal ulcer. Needless to say, the symptoms of anemia have not returned since proper medical management of the ulcer. I feel sure the primary condition requiring treatment was the duodenal ulcer. Of course, iron therapy was a desirable supplement. In this connection, it should be remembered that certain forms of iron are incompatible with alkalies which are commonly used in ulcer treatment. For example many physicians still prescribe iron and ammonium citrate. This in combination with alkalies results in an inert iron compound.

In the two following cases, I am pleased to state that the proper diagnosis was made more promptly. Both cases illustrate how failure of diagnosis would result in wrong therapy.

Case 2.—In July, 1935, Mrs. L. B., a thirty-four year old white woman, was seen with the complaints of fatigue and lack of energy, cramps and aching of the legs, numbness of the entire right side and swelling of the eyes, tongue, hands, ankles and abdomen, all of about one year's duration. Physical examination revealed a slightly obese, young adult woman appearing pale and chronically ill. The eyelids were puffy; there was a generalized dryness and roughness of the skin. A blood count revealed a hemoglobin of 57 per cent by the Sahli method and a red blood count of 3,200,000. A metabolism test was minus thirty-six. The patient has taken thyroid ever since in doses varying from one to three grains daily. The symptoms were all improved and the anemia has not returned. While the mechanism of the etiology of anemia in myxedema and hypothyroidism is yet a controversial matter, it is definitely established that such an anemia does not respond to iron, liver, or vitamin therapy but does respond well to thyroid medication.

Case 3.—In February, 1939, Mr. B. B., a forty-two year old white man, was seen with the complaints of feeling generally under par and easily tired. He also complained of slight aching in the left lower quadrant of the abdomen and of itching of the rectum. Physical examination was entirely negative except for slight tenderness over the region of the descending colon and a small rectal fissure. A blood count revealed a moderate anemia. Stool examination revealed a strongly positive benzidine test and also the ova of pinworms. Pinworms were also found in specimens from the wife and one child.

Proper treatment for the anemia in this case, then, consisted of specific treatment for pinworms rather than the prescribing of a "gunshot" anemia mixture. The anemia of hookworm, tapeworm and malaria are so common in the south that I mention them merely in passing.

With the multitude of anemia mixtures flooding the pharmaceutical market, there must be too many such prescriptions given without an etiologic diagnosis. From the three case abstracts given, it can readily be seen that a complete "gunshot" anemia medication would have to contain not only iron, liver, vitamins but also thyroid, anthelmintics and antacids. One, then, might also add the newer vitamin K with bile salts for the postoperative bleeding and anemia of jaundiced patients, *et cetera*. In the words of Dr. Russell Haden, it would indeed be a "dash of this and a

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dash of that". If the necessary ingredients were contained therein the amounts would no doubt be inadequate. The cost would necessarily be high as compared with that of specific medication and many patients could not afford to pay for the medicine without perhaps cutting their food budget and subsisting mainly on beans, rice and potatoes. And a poor diet in itself is a frequent cause of anemia. The diet should include red meats and liver and foods rich in vitamins and minerals.

Several patients have come under my observation suffering from pernicious anemia, who have been properly diagnosed but treated with inadequate amounts of liver extract. It should be remembered that liver extract is much more effective when given intramuscularly. Nor is there any rule of thumb to apply as to adequate dosage. The individual variation is great. The patient must be sold on the importance of occasional blood check-ups just as the diabetic patient must be sold on the value of frequent urine tests. The relapse is often insidious and each time more likely to result in spinal cord damage. A person with pernicious anemia should be frankly told it is a life-time ailment and not at all "pernicious" in the light of our present-day knowledge, unless neglected. In connection with any discussion of pernicious anemia, it should be stressed that gastro-intestinal malignancies may closely simulate this disease and should be carefully ruled out before treatment.

In our search for disease, we must always remember the common physiologic causes of microcytic iron-deficiency anemia. This is especially true in women. The bleeding of menstruation results in an iron loss which not infrequently must be supplemented. The iron requirement during pregnancy is greatly increased. Several careful clinical studies have shown the high incidence of anemia during pregnancy; yet I believe that too many physicians check merely the blood pressure and urine during the prenatal period with little heed to the hemoglobin. The routine of prescribing iron during pregnancy no doubt has great merit unless the red blood cell count and hemoglobin value be regularly checked. Careful attention to diet should here be stressed, for food aversions, nausea and vomiting are common in pregnancy. Most of us, who practice internal medicine, exclude obstetrics but we often have opportunities to make suggestions to our colleagues who are fond of this sort of night life. Often general practitioners and obstetricians become alarmed over the development of a hemic heart murmur resultant from the anemia of pregnancy. The reference to us for a heart examination then presents us with a golden opportunity to stress the strain of pregnancy on the poor iron reserve of the body and the frequency of iron-deficiency anemia of pregnancy.

Just one step beyond the physiologic causes are the pathologic conditions, in themselves often insignificant, resulting in chronic bleeding and depleting the iron storage of the body. These are often insidious and not alarming to the patient and thus easily may escape the attention of the physician. Non-painful bleeding hemorrhoids, menorrhagia, metrorrhagia and bleeding gums are here the chief offenders. Many women have excessive menstrual bleeding without realizing the fact. Again at menopause, women expect unusual variations and some will ignore profuse bleeding or the passage of large clots partly because of the unfortunate myth of woe woven around that "change of life". They are martyrs to their fate and stolidly will accept the ordeal, come what may. Then, too, many women are possessed with what I choose to call a false sense of modesty (perhaps an admirable trait). They dare not mention their monthly curse even to their physician. It, therefore, must be the duty of the physician always to inquire for the specific details of vaginal bleeding, quantity, frequency and the passage of clots.

Given a patient with anemia, the history of occupation is indeed important. For many of the occupational anemias a change of work is imperative. Traffic officers in the cities may suffer from chronic carbon monoxide poisoning, with either anemia or polycythemia. Painters and other workers with lead may pass their tolerance. Employees of chemical plants must be carefully guarded against over-exposure to many agents which are toxic to the hematopoietic system. Roentgenologists and x-ray technicians frequently develop a marked depression in the function of bone marrow.

Various blood dyscrasias and lymphatic diseases produce marked anemias. Hodgkin's disease, lymphosarcoma, and leukemia are the best examples of this group. While most of this class of diseases are incurable, early diagnosis and x-ray therapy offer much in the way of amelioration. On the other hand, random prescriptions for the obvious anemia merely delays the diagnosis and lowers the hope of prolonging for a while a comfortable existence.

One could list many more causes of anemia with various types of therapy indicated. This paper is presented chiefly in the hope of stimulating the desire for a more careful history and examination in patients with anemia, that the etiology may be definitely determined. Treat-

ment then will be specific, adequate, and results more lasting. Druggists can easily dispense "gun-shot" anemia mixtures, well within the limits of our liberal democratic laws. Our task lies beyond that. In the treatment of all cases of anemia let us think of ourselves as detectives in search of the cause rather than the prescribers of pink pills for pale people.

DISCUSSION (*Abstract*)

Dr. L. W. Diggs, Memphis, Tenn.—One of the common errors in the diagnosis of anemias is in the method of estimation of hemoglobin. The Tallqvist instrument, while having its place in telling the presence or absence of anemia, is not sufficiently accurate for differential diagnosis of the type of anemia, color index, and so on. The Sahli instruments using the acid hematin method are usually fairly accurate provided the newer models purchased from reliable manufacturers are used. Older instruments and instruments of lower price are likely to be grossly inaccurate. At the University of Tennessee we standardize hemoglobinometers each quarter, using the van Slyke manometric methods to make up standards, and find that the hemoglobinometers are often inaccurate to the extent of 20 per cent and sometimes as much as 50 per cent. The use of various types of cylinder for a single standard, as is often done in hospital practice, is unreliable and should not be permitted. The best methods for a hospital are the photelometer, the Haden-Hausser and the Newcomer. Hemoglobin should be expressed in grams rather than in terms of per cent, for there is no such thing as one value's being normal for all ages and sexes and for all environments. A child with a hemoglobin of 10 to 12 grams is normal, whereas this is a low-grade anemia for an adult male. The expression of hemoglobin in grams allows one to calculate the mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration which are more dependable values than the color index and saturation index.

Another common error in technic is the failure to study and to describe the erythrocytes as seen in the blood smear. We are accustomed to consider the differential white cell count as the most important part of the smear examination and are inclined to forget that red cells and platelets also constitute a part of the picture. Repeatedly we see pernicious anemia, sickle cell anemia, malaria, lead poisoning and other diseases missed because the physician or technician failed to examine the red blood cells.

There does not exist a single classification of anemias which is entirely satisfactory. We prefer to use all classifications. In appraising an anemia an attempt should first be made to discover the cause. Here the dietary history, the occupation, the family history, history of blood loss or infection, the examination of stool for occult blood, and the physical examination are of value. Next we determine whether there is increased blood destruction. Here the icteric index, van den Bergh examination, and examination of urine for urobilin are of value. Defective marrow regeneration is detected by means of the reticulocyte count, smear studies and in difficult cases bone marrow biopsies. The size and hemoglobin content of the cells and the determination of the mean corpuscular values aid in diagnosis and in the directing of therapy, for anemias of a macrocytic hyperchromic type are more likely to respond to liver, whereas anemias in which the cells are microcytic and hyperchromic are best treated by iron. It must be remembered that anemias may be due to multiple causes. Thus a patient with pernicious anemia may have blood loss and iron deficiency, or a patient with hemolytic jaundice may be on a defective diet or have a chronic infection.

In treatment one of the errors is the use of arsenic. Arsenic in small doses does cause the appearance of reticulocytes in larger numbers in some anemias, but the drug is toxic and tends to depress normal bone marrow activity rather than to stimulate it in a normal manner. Another treatment error is to use transfusion when liver or iron or simple diets would be sufficient. The transfusion of patients with terminal anemia and with edema and myocardial failure often leads to circulatory failure unless the blood is given very slowly and in small amounts.

THE SIGNIFICANCE OF MACROCYTOSIS IN NEUROPSYCHIATRIC PATIENTS*

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and
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Since March, 1938, we have made certain clinical and laboratory observations which tend to show that the familiar dietary limitations in psychoneurotic patients are accompanied almost characteristically by enlargement of the red cells as shown by the laboratory estimation of the mean corpuscular volume. Further studies have also shown that this change in the red cells is favorably influenced by the administration of vitamins, probably principally the vitamin B complex, these changes measured by the same test. The method used was selected because, as advocated by Wintrobe,[1] it appears to be a simple and reliable index to the size of the erythrocytes. No complex hematologic studies have been made, these being too far afield for the purpose of this study. The upper index of normal has been established in this locality to be in the neighborhood of 90 cubic microns, which is in essential agreement with the findings of Wintrobe.[1]

Our interest in this matter was stimulated by observations made on the following patient:

Case 1.—C. H., aged 40, a salesman, entered the hospital March 15, 1938, referred by Dr. Robert Short. He complained of headache, slight fever, night sweats, loss of about 20 pounds in weight, and generalized weakness. These complaints followed an attack of influenza in December, 1937.

The patient told us: "When I was a kid they had to give me bromides; I was always nervous; I got better

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for a while, but I never have been any good since I had mumps." The attending physician said that the patient had always been of an anxious, apprehensive type. Frequent vague gastro-intestinal pains had been present over a long, indefinite period; at one time, an unconfirmed diagnosis of gastric ulcer had been made. At all times the patient had limited his diet until at the time of examination he said: "I am almost afraid to eat anything."

Outstanding findings in the physical and neurologic examination were as follows:

There was a marked increase in sweating reactions; fibrillary tremor, more marked on the left and intensified by purposive action. His deep reflexes were hyperactive, more marked on the right. The Babinski was positive on the right. Vibratory and position sensibility were reduced in both great toes. There was a poorly sustained bilateral ankle clonus.

The Romberg was positive, falling backwards and to the right. His gait was halting and insecure, without characteristic ataxia.

The tongue showed slight tremor and was quite red with no coat. Other neurologic findings were not significant.

Gastric analysis showed total acid of 65°, free acid of 39°. Red cells on March 18, 1938, were 4,760,000, with mean corpuscular volume of 117.6. There was considerable doubt as to the diagnosis in this case. The hematologic findings were not characteristic of pernicious anemia; this doubt was further reinforced by the gastric analysis. Consultation with Dr. J. M. Hill, Director of the Baylor Hospital Laboratory, resulted in his suggestion that the macrocytosis might be due to vitamin deficiency. Accordingly, the patient was placed on a high vitamin B diet, with yeast extract, vitamin A, B, D capsules, and liver extract intramuscularly daily.

Clinical improvement in all symptoms was quite rapid. On March 25, 1938, seven days later, red cells were 5,660,000 and mean corpuscular volume had dropped to 84.6. He subsequently made an uneventful recovery, returned to work, but continued to be "nervous."

The sharp, prompt return of the red cells to normal size suggested to us that the test might be used as a qualitative determinant for the presence of vitamin deficiency.

It was pointed out by Minot and Murphy[3] in 1926 that dietary deficiencies may become manifest in the blood picture. Normally the size of the red cell is remarkably constant. It has been said that the size of a man's red cells remains in health as constant as his finger prints. In disease affecting erythropoiesis, imperfectly formed cells are turned into the circulation, and the manner in which the red cell is abnormal may indicate the manner in which erythropoiesis is disturbed. Thus in the iron deficiencies, cells with inadequate hemoglobin are produced; they probably withstand trauma inadequately, possibly breaking up into small cells or microcytes.

When the essential hematopoietic principle or antipernicious anemia factor is deficient, the familiar picture consisting of macrocytic cells with normal concentration of hemoglobin, with variations in size, shape and staining reactions, is found. Estimation of the size of the red cell has, therefore, been of importance in the differential diagnosis of the anemias. It is beyond the scope of this paper to go further into the consideration of the anemias in general.

Of interest, and related clinically, are the studies of Elsom and Sample[4] on the macrocytic anemias in pregnant women. Significantly in these studies, the administration of brewer's yeast and liver extract effected relief from the characteristic clinical changes, paresthesia, fatigue, edema, gastro-intestinal symptoms, impaired vibratory sense and tachycardia. Also, and in relation to our own studies, they noted a reduction in the mean corpuscular volume among the favorable blood responses. The authors conclude that the clinical and hematologic findings reported were due to a deficiency of vitamin B.

The concomitant occurrence of psychoneurosis and dietary deficiency has also been pointed out by Wexberg.[5] Winans and Perry[6] have summarized this phase of the problem by the statement: "Any prolonged illness accompanied by reduced food consumption might be expected to produce the disease."

The following cases are summarized to show the relationship between dietary history of deficiency, the marked increase in the size of the red cells, and the response to vitamin therapy.

Case 2.—Mrs. C. E., aged 24, had been married seven years and had no children.

Her complaints were: "Fallen stomach, catarrh of the gallbladder, overactive thyroid, nerves were shot, shortness of breath and fatigue." For three years she had been very nervous, afraid of heart trouble and impending death. Food soured on her stomach with occasional vomiting.

Her life as a child was unsatisfactory. Her parents were separated, she had no home, and lived with various relatives. Her husband was not affectionate or attentive. Intercourse made symptoms worse. The patient was taking eight different medicines for various symptoms.

Physical and neurologic examinations were negative except for moderate emaciation and moderate tachycardia. The tongue showed moderate reddening and slight coating. The deep reflexes were moderately and equally hyperactive. The patient belched frequently, seemed tense and apprehensive, seemed not to tire of relating her symptoms.

My opinion was that she was suffering from (1) psychoneurosis, and (2) avitaminosis.

Treatment consisted of psychotherapeutic interviews about twice a week for 2 or 3 weeks, once a week for 2 to 5 weeks, then at irregular intervals for discussion. She was given yeast extract and a liver and stomach extract with iron and vitamin B.

Marked improvement was noted. The patient is now eating a general diet, and adjustment is quite satisfac-

BLOOD EXAMINATION

At First Visit		*After 18 Weeks of Vitamin Therapy*
Red cells	4,690,000	4,630,000
White cells	4,900	
Mean corpuscular volume	109	91 cubic microns
Hemoglobin per cent	100	

tory. Anxiety and tension have subsided to a marked degree.

Case 3.—Mrs. C. S. C., aged 29, had been married for eight years. She complained of nervousness and depression.

Her stepfather had had a nervous breakdown 6 weeks previously, and had gone to a sanitarium. Since that time the patient had been afraid she would "go crazy." She interpreted her nervous feelings as onset of insanity. She improved somewhat at times.

She said that house work irritated her and food nauseated her. She did not "get along with her mother." Her mother quarreled with the patient and her stepfather.

The patient said she noticed nervous symptoms before her marriage. For several months she was depressed and nervous. She had been to many physicians.

Sexual relations were not altogether satisfactory, due to differences in sexual desire.

She thought she might be pregnant now, wanted another child, but feared it would be "crazy."

Physical and neurologic examinations were negative. The patient appeared well nourished, there was moderate acne, and slight increase in hair growth around the face and nipples.

BLOOD EXAMINATIONS

At First Visit		*After 6 Weeks of Therapy*
Red cells	4,500,000	4,610,000
Hemoglobin per cent	85	90
Mean corpuscular volume	113 cubic microns	95 cubic microns

The Wassermann (Kolmer) was negative.

Our opinion was that she was suffering from a psychoneurotic depression.

Treatment consisted of giving her (1) vitamin A, B, D capsules and (2) psychotherapy about once a week for 8 to 10 weeks.

The patient markedly improved and has resumed her normal duties. Her depression has lifted entirely.

These two patients further emphasize the possible important relationship between emotional and personality factors, diet and the red cell response. It must, of course, be kept in mind that the amelioration of symptoms in these patients is subject to suggestion as well as other psychotherapeutic factors; the laboratory tests of the size of the red cells is not, probably, directly or promptly subject to these same considerations. Consequently, it is our feeling at this time that a bilateral attack on such problems must be made, and that neglect of either orthodox psychiatric principles or of the attending physiologic factors must lead to disappointment in results.

Patients whose dietary histories were not affected by the psychiatric picture showed a definite tendency toward normal blood pictures.

Case 4.—Mrs. E. G. N., a housewife, married 5½ years, had two children. She was referred by Dr. Howard Crutcher for office consultation.

Her complaint was: "I have a desire to kill. I think I'm going crazy; thinking of committing suicide."

She gave a history of obsessive thinking over a period of two years, thoughts of killing her little girl, her husband, herself. There had been no attempts to carry out these fantasies. Her appetite had been good and there were no limitations in her food intake. She felt loss of interest, depression, seclusiveness. She had always been a meticulous wife. Disorder worried her. She was unresponsive sexually.

She gave a past history of insecurity in childhood, due to constant friction between her father and mother.

Physical examination was not significant. Her mean corpuscular volume was 91 cubic microns.

This patient did not remain for psychiatric treatment and has not been followed.

Case 5.—C. A. McG., aged 32, complained: "I'm ashamed I'm as scared as I am. It's an obsession. I get scared of these storms. I've always been afraid of appendicitis. I got a pain or two and thought I had appendicitis. I keep away from windows so I can't see the clouds."

The remainder of the case record shows a classical, obsessive, compulsive neurotic in excellent physical condition, his dietary history perfectly normal.

The mean corpuscular volume was 90 cubic microns. The patient has been on psychotherapy at irregular intervals, is making a fairly satisfactory adjustment, but is still quite compulsive.

To what extent the genesis of symptoms from the original personality disorder, dietary factors, blood picture changes with eventual somatic response may go, would be difficult at this time to evaluate.

The following case, however, illustrates an extreme example:

Case 6.—Mrs. W. H. C., aged 36, a housewife, married, complained of numbness and tingling in the toes and difficulty in walking.

For appoximately one year the patient had noted increasing weakness, stiffness and unsteadiness of both legs, with tingling, numbness and "drawing pain" in the back.

Her past history was inadequate as to detail. It consisted chiefly of drifting from physician to physician with a multiplicity of symptoms, many of them gastro-intesti-

RED CELL VOLUME AND EFFECTS OF TREATMENT

Patient	Diagnosis	Dietary History	First Reading	After Therapy	Clinical Status
Mrs. D. M. K.	Chronic alcoholism, psychoneurosis, avitaminosis	Positive	113	98	Improved
T. A. C.	Psychoneurosis (reactive depression), avitaminosis	Positive	131	101	Improved
Mrs. R. R. H.	Psychoneurosis, avitaminosis	Positive	104	102	Improved
G. F. W.	Hypothyroidism, avitaminosis	Negative	130	97	Improved
J. W. L.	Psychoneurosis (neurasthenia), avitaminosis	Positive	130	116	Improved
Mrs. C. E.	Psychoneurosis, anxiety state, avitaminosis	Positive	109	91	Improved
Mrs. C. C. C.	Psychoneurosis (reactive depression), avitaminosis	Positive	113	95	Improved
Mrs. H. A. S.	Polyneuritis	Negative	113	86	Recovered
C. H.	Psychoneurosis, avitaminosis	Positive	117	84	Improved
Mrs. W. H. C.	Psychoneurosis, combined cord lesion, avitaminosis	Positive	111.1	103.1	Improved

nal, and marked gradual limitation of diet as a result of blaming one food after another for the symptom. Her home situation was poor, consisting of conflict with her older daughter, and little respect or liking for her husband.

The neurologic picture, briefly, was that of combined lesions of the posterior columns and pyramidal tracts, involving chiefly the lower extremities, but showing some signs of involvement above the cervical segments.

On November 19, 1938, the red count was 2,700,000, and mean corpuscular volume 111.1, with no other characteristics of a primary anemia. Gastric analysis showed total acid 5°, free acid 0°.

On December 2, 1938, after intensive treatment with liver, yeast and nicotinic acid had been in progress since November 21, the red cells had increased to 3,330,000 and the mean corpuscular volume had dropped to 103.1. She was discharged from the hospital at that time and no further laboratory work has been done. Clinical improvement has continued; when the patient was first seen she was bedridden; at the present she is able to do moderate housework.

Although cases of this type raise the question of pernicious anemia, certainly the picture was not classical and the long dietary history cannot be ignored.

Observations made on the above patients, as well as others not reported in detail, led us to feel that more extensive use of the mean corpuscular volume as a laboratory test would prove helpful clinically and lead eventually to conclusions as to the value of the procedure in confirming the presence of avitaminosis.

While we have not been able to obtain routine tests on all patients seen, a large number of tests have been made on a rather wide selection of patients. The majority of these patients have been ambulant, mostly the routine office patient, a high proportion of whom are psychoneurotics. Sixty-six patients were tested. Of these, 38 had a mean corpuscular volume above 95; 28 showed readings below 95. The highest reading was 132, the lowest 74. Detailed studies of these cases will be the subject of another report.

Of the patients showing high readings, ten have been tested following a period of therapy. The table above shows certain significant features in these cases.

The most significant feature in this group of patients is that all but two of the patients reported definite limitation of diet. These patients all show a marked elevation in the mean corpuscular volume and following a high vitamin intake, in each case, there was seen a lower reading.

SUMMARY OF OBSERVATIONS AND CONCLUSIONS

(1) A general tendency toward macrocytosis has been observed in patients who have varying types of nervous and mental disturbances.

(2) This tendency is more marked in patients whose dietary histories show restriction from any cause. This tendency was not observed in patients whose dietary histories were negative, unless other comparable factors were present, such as other metabolic disturbances.

(3) Macrocytic changes, as shown by the mean corpuscular volume, tended to regress under vitamin therapy in every case.

(4) The macrocytic changes were seldom accompanied by the gross changes of secondary anemia.

(5) The changes due to vitamin deficiency could not be demonstrated by red blood cell counts and hemoglobin determinations alone.

(6) Adequate psychiatric therapy appeared to be more effective if supported by adequate vitamin therapy.

(7) In the opinion of the authors the mean corpuscular volume may be used as a confirmatory qualitative test for vitamin deficiency.*

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DISCUSSION (*Abstract*)

Dr. Raymond S. Crispell, Durham, N. C.—The paper which we have just heard deals with three rather complicated and confusing subjects: hematology, the vitamins and neuropsychiatric disorders and their interrelationships. Each one of these subjects is involved and obscure, and when they are all implicated in a discussion, the complexity and confusion are greatly increased and compounded.

Drs. Witt and Cheavens suggest that an avitaminosis or a hypovitaminosis causes a macrocytosis and that neuropsychiatric patients are apt to restrict their diets and to get into a state of hypovitaminosis with a resultant macrocytosis; or clinically, the other way round, that a macrocytosis is often found in mental and nervous patients, and that when it is found it reflects a hypovitaminosis and that both the macrocytosis and the neuropsychiatric disorder are improved, if not cured, by appropriate psychiatric therapy plus adequate vitamin therapy. They intimate that in the presence of a macrocytosis (which they say indicates a vitamin deficiency) adequate vitamin therapy makes possible more effective treatment.

The knowledge and concepts of hematology and vitaminology are rapidly developing and shifting. The neuropsychiatrist finds it difficult to keep up with the developments in neuropsychiatry. He finds it very difficult to keep up with the advances and progress in the other two fields of hematology and nutrition.

As far as I can learn, the hematologists have found no definite or specific relationship between a vitamin deficiency and a macrocytosis, especially a hyperchromic macrocytosis. They do say that dietary deficiencies are apt to cause a hypochromic or secondary anemia and that in a few incidences it is possible for the hematopoietic system to be depressed with a resultant macrocytosis. But apparently they do not seem to be sure, in such a situation, whether the macrocytosis is due to a vitamin deficiency or to deficiency of other substances such as iron or protein. Apparently the question is begged in all the hyperchromic macrocytic anemias, including the one that we have known as Addison-Biermer's or pernicious anemia. The latter and all of the macrocytic anemias are referred to as anemias in which fractions of liver soluble in 70 per cent alcohol are beneficial, or anemias due to lack of the "intrinsic factor." Investigators hedge as to whether or not improvement with the use of liver is due to vitamins or to other factors in the liver substance which are not vitamins as we know vitamins. Perhaps the improvement comes about because of a combination of vitamins and other material in the liver substance.

The first case cited by Drs. Witt and Cheavens showed macrocytosis since the mean corpuscular volume was 117.6; but it had not the criteria or picture required to diagnose pernicious anemia. Judging by the hyperactive and unequal deep reflexes, the impairment of the vibratory and position sensibilities, the poorly sustained bilateral ankle clonus, the faltering gait and positive Romberg, there was a neurologic involvement. Probably there can be neurologic and psychiatric involvements and complications in anemias other than those which we know as pernicious anemia, both in hyper- and hypochromic and macro- and microcytic anemias, and possibly these anemias are caused by a vitamin deficiency. But neither proposition has been established in medical teaching or medical literature. This contribution of Drs. Witt and Cheavens is a good start toward doing so.

In the first two cases cited, reddening of the tongue was mentioned, which suggested the possibility of subclinical pellagra. Sometimes a macrocytic, as well as the more usual "secondary" or microcytic anemia, is found in pellagra (as it is also in pregnancy, as Drs. Witt and Cheavens mentioned); and all of the forms of anemia encountered in pellagra respond to the correct and adequate treatment of this condition, especially by the use of liver. Subclinical pellagra is not well understood or well recognized. Perhaps there was an element of this condition in some of the other cases mentioned.

It seemed to me that *Case 6*, with signs of subacute combined sclerosis, was a case of pernicious anemia, although it was not altogether typical and did not fulfill all the criteria for this disease. The dietary restrictions may have increased or accelerated the picture of pernicious anemia, but it is doubtful that they alone caused it. Incidentally, we must remind ourselves that while pernicious anemia seems to be a deficiency disease, it has not been established that it is primarily a vitamin deficiency. It is a disease essentially improved by liver substance, in which the addition of vitamins other than those in liver substance is helpful. The neuropsychiatrist should become thoroughly familiar with pernicious anemia, since sometimes the neurologic or psychiatric symptoms and signs are the first to occur and are the predominant ones. The blood picture and findings of pernicious anemia may be masked and less prominent and less easy to determine and to diagnose than the neuropsychiatric picture.

The salient points brought out by Drs. Witt and Cheavens bear repetition. Many neuropsychiatric patients, especially many psychoneurotic ones, will, and do, restrict their diets, and thereby they are liable to have a greater or less degree of dietary deficiencies, vitamin and otherwise. It is interesting and instructive to learn that these deficiencies are often manifested by macrocytosis as indicated by an increase in the mean corpuscular volume of the blood, and that there can be a striking improvement not only as to the macrocytosis, but also in the neuropsychiatric symptoms, by the use of liver and vitamins. We are hoping that Drs. Witt and Cheavens will follow through and eventually be able to tell us specifically which vitamins are at fault and which ones are qualitatively and quantitatively to be used in the treatment of the conditions. Further work may scientifically establish the relationship between the vitamin B complex deficiencies and macrocytosis which this communication suggests.

Besides the anemias caused and cured by vitamin B deficiencies and by liver substances, the hematologists talk about vitamin C anemias, both clinical (scurvy) and subclinical, which are cured by vitamin C therapy. They say that these anemias may sometimes, though rarely, be macrocytic.

At present, I believe the hematologists are inclined to think that the loss and perversion of appetite in neuropsychiatric and especially in psychoneurotic patients, causes the deficiency, and that the vitamin therapy corrects the deficiency rather indirectly by stimulating the appetite than directly by stimulating the hematopoietic system; in other words, that there is no specificity but a multiplicity of factors causing the conditions and improving them.

Unfortunately for the argument of this paper, the hematologists do not readily recognize or talk about, except of course in the case of pernicious anemia, the neuropsychiatric and especially the psychoneurotic symptoms encountered in macrocytic and various other forms of anemia. Perhaps this is due to a blindness of the hematologists to neuropsychiatric and psychoneurotic symptoms and signs.

In some ways, those of us who were medical students and interns before the days of the hematocrit indices were lucky. For the benefit of those of us who were medically reared before the advent of the newer hematologic enlightenments, perhaps Drs. Witt and Cheavens should have included in their description of the blood of their patients the color indices and the blood pictures as seen on the stained microscopic slide.

I think one of the most valuable things that we can learn from this paper is that we neuropsychiatrists must never fail to be good internists and diagnosticians and that we must never neglect to study our patients from the standpoint of internal medicine and to obtain all the necessary laboratory examinations. I am sure that with the hint and information which has been given to us here, we shall be more careful about inquiring as to the dietary histories of our patients, and when there is a suspicion that they have been deficient we shall be doing more careful blood work and, specifically, more mean corpuscular volume determinations on our patients, and we shall even more routinely use additional vitamin therapy to support the whole treatment of our patients in order to render it more effective.

If we overemphasize and rely solely on the psychogenic approach, we stand in danger of losing our standing as physicians and alienating ourselves from the internists. At the same time, I heartily agree with Drs. Witt and Cheavens, and I cannot help repeating their conclusion that the double approach, psychogenic and physiogenic, is indicated and necessary in most of our neuropsychiatric and especially in our psychoneurotic cases. We are pleased to think that there is less neglect of the physiogenic among neuropsychiatrists than there is of the psychogenic by the internists.

I am sure that the communication and contribution of Drs. Witt and Cheavens which has just been given is very valuable and stimulating, and that with or without the aid of the internists and hematologists we neuropsychiatrists will set to work and eventually determine the relationships, diagnostic and therapeutic, between certain obscure neuropsychiatric and certain obscure hematologic conditions.

Dr. Lewis A. Golden, New Orleans, La.—The paper of Drs. Witt and Cheavens is important in that it calls to our attention the belief that an increase in the mean corpuscular volume, in the absence of obvious anemia, may be used as objective confirmation of our suspicion that a nutritional deficiency may be present in our nervous and mental patients. Obviously it is necessary to know this, since it is our objective in treating nervous and mental patients to remedy any physical disorder which may be a contributing factor to the total picture.

The paper raises, however, many other interesting points for discussion. The cases used as illustrations by the authors show moderate and severe neurologic changes which are attributed by Drs. Witt and Cheavens to the presence of a vitamin deficiency. Such neurologic changes bring us at once into an arena of conflicting opinions as to exactly what happens to the nervous system when a vitamin deficiency is present. Unfortunately, that question has not been settled to the satisfaction of hematologists, clinicians or neurologists. I would suggest, without criticism, however, that the neurologic examinations included in this paper are not detailed enough to allow one to be absolutely certain that the clinical neurologic picture is entirely due to vitamin deficiency. Unfortunately, a macrocytosis occurs in many other diseases and does not in itself mean nutritional deficiency. Macrocytosis may occur in a wide range of conditions, and somehow produces deficiency in erythrocyte maturing factor.

The question as to how a nutritional deficiency revealed by a macrocytosis contributes to the entire picture of the psychoneurotic is difficult to analyze, as, conversely, it is difficult to evaluate the relative importance of supplying sufficient vitamins to the disappearance of psychoneurotic complaints. It is known that nutritional deficiency is often associated with certain symptoms such as anxiety, restlessness, insomnia, and thus it may be difficult or confusing to ascribe these clearly on the basis either of a deficiency or on the basis of a psychoneurotic state.

In regard to the more serious neurologic findings reported by Drs. Witt and Cheavens, one must confess that there is at present no unanimity of opinion as to what kind of pathologic lesion is present in the nervous system in nutritional deficiency and how it compares to that seen in pernicious anemia. It is true, however, that clinically neurologic cases produced on the basis of nutritional deficiency will clear very rapidly with the addition of the deficient vitamin. For example, I have had the repeated experience of seeing a dog fed with dried milk plus bone powder develop spastic paraplegia which would miraculously clear up in a period of one or two days on the addition of brewers' yeast. Obviously such an apparently severe neurologic change must be entirely different from that in association with pernicious anemia, and yet dietary deficiency or rather vitamin B_1 deficiency, has also been blamed for the production of neurologic changes in pernicious anemia.

Time limits the points that may be raised in this discussion. I hope, however, that Drs. Witt and Cheavens will continue this interesting investigation, using a larger number of controls and giving us more detailed neurologic analyses for our consideration.

Dr. Witt (closing).—I wish to agree with Dr. Crispell's suggestion that in all likelihood many of these early cases are subclinical pellagra. In a few of them, not enough to record, we have noted a red tongue, a beginning discoloration of the knuckles, some little rustiness and discoloration of the elbows and, strange to say, significantly, I believe, along with a generalized hyperreflexia, complete absence of abdominal reflexes.

We are not in a position to determine exactly which vitamin is the offender, and I doubt very much that in many cases one vitamin is the sole offender. There are shotgun vitamin prescriptions which I am certain, at least for the present, we shall feel safer in using.

I do not believe it will ever be possible to separate or eliminate psychotherapy in the treatment of psychoneurotics.

The principal point that we wished to bring before you is that the determination of a mean corpuscular volume is a relatively simple laboratory procedure. It is much more generally available than are the necessary procedures for more extensive hematologic investigation.

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EXPERIMENTAL INTERSEXES

For many years it has been the complaint that the mountain seemed to have labored and brought forth a clinical mouse in the field of androgen (testicular hormone) and estrogen (ovarian hormone) therapy, and specific therapy with these chemicals seems still a little mousey. At least the mouse is not absolutely sure which way to run.

Physiologically potent hormones have for some years been purified, standardized, crystallized, and synthesized. It has been established that they control plumage, hair distribution, voice, maternal and paternal instinct, and genital and mammary development in lower and higher animals. The anatomical effects of androgens and estrogens are to a considerable extent antagonistic; yet both ovarian and testicular hormones are normally found in human blood and urine of both sexes at all ages. Before puberty, girls tend to excrete more androgens than do young boys, and men and women excrete about the same quantity.[1] The explanation of their production by both sexes without confusion of the secondary sex characteristics may lie in differences of their metabolism, or in the presence of antihormones or inactivators.

Innumerable clinical studies with the gonadal hormones have been enlightening; yet their role even in uterine bleeding is not yet clear. The onset of bleeding may be produced in several ways. One is by treatment with estrogens. Testosterone in the human being brings about atrophy of the uterine lining and mammary glands, and has been employed for control of bleeding. Estrogen stimulates proliferation of the uterine lining and mammary glands, and has also been used to control bleeding. Clinically, estrogens have been employed for two opposite purposes: to initiate and to stop bleeding. Testosterone injections in experimental animals increase kidney weight, and it has been suggested that they may improve kidney function.[2] The increased concentration of estrogen in human blood and urine in pregnancy are well known, its purpose obscure.

The effects of injection of either androgens or estrogens in pregnant animals have been studied recently by a number of workers.[3] The sex of the litters may be varied by two means. An apparently increased number of male animals may be obtained by treatment with testosterone, and of females by estrogens, in small mammals and amphibians; and intersexed or hermaphrodite animals may be produced by both methods.[3] This was first reported in 1936.

Greene, Burrill and Ivy,[4] of Chicago, note that if androgens are administered to pregnant rats early enough in gestation and in considerable quantity, all the animals in the litters appear to be males. On close study, marked developmental abnormalities are detected. The tendency to masculinization was greater the earlier the injections were begun. If either estrogens or androgens were given late in pregnancy or to the young immediately postpartum, gross abnormalities in the female were produced, with hypo-

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spadias, arrest of general development, and inhibition of development of the ovarian capsule.

Confirmation of the disturbing effect of antenatal androgens and estrogens on the anatomy of the reproductive tract has been so general that one cannot but wish to carry the investigations into the human field, to learn why early diagnosis of sex of the offspring by studies of the hormone level has not been possible, and what happens to the large quantities of estrogen which are produced during pregnancy and which do not feminize the male fetus. In the presence of the excess estrogens of human pregnancy, some explanation is needed of the reason why all men born of women are not female.

A low estrogen level has been reported in certain toxemias of pregnancy, and therefore one might expect more male babies to be born after a toxemic pregnancy. It has been suggested that this type of toxemia is benefited by injections of estrogens. One might therefore search for signs of hermaphroditism or of genital maldevelopment in the offspring of women so treated. These have not been reported. Diabetic pregnancies have been reported to be not uncommonly low in estrogen; yet increase in the proportion of male offspring from diabetic mothers has not been reported.

The hormone level should be intimately concerned in the production of human intersexed individuals; and diagnosis of hermaphroditism *in utero* should eventually be possible, with hope of its antenatal correction.

In considering the difficult operations at times undertaken for correction of developmental abnormalities of this type, one wonders whether, if they were discovered in the newborn, they might be corrected even in this period with hormone therapy rather than subsequently by surgery in the adult.

SULFATHIAZOLE

Therapeutic successes with sulfanilamide and sulfapyridine, two compounds of this class now licensed for distribution by the Federal Trade Commission, have whetted the medical appetite for still more chemicals with specific antibacterial and few toxic effects; and many laboratories are attempting to supply the demand. Fosbinder and Walter[1] and others prepared and investigated the activity of several sulfathiazole and similar compounds last year, and reported that the former possessed antistreptococcal and antipneumococcal activity.

Structurally, the sulfathiazoles are depicted as analogues of sulfapyridine. Sulfanilamide is a single benzene ring with attached sulfur and nitrogen radicals. Sulfapyridine is the same sulfanilamide to which had been added a second 6-sided ring, a pyridine, or nitrogen-containing, ring. Sulfathiazole is sulfanilamide with an added five-sided ring containing as much nitrogen as sulfapyridine and more sulfur. The thiazole ring may be variously modified with methyl and phenyl groups.

McKee and associates[2] have compared the toxicity of sulfathiazole and sulfapyridine in mice. They say that sulfathiazole resembles sulfapyridine in its efficacy against the pneumococcus and other infections in mice. Both it and sulfapyridine have an appreciable effect against the agent of lymphogranuloma venereum.[3] Neither had any activity against swine influenza or herpes simplex. Because the compound disappears rapidly from the blood, and there is some difficulty in its absorption from the stomach, it was given by McKee and associates[3] to animals mixed with their food, as 1 per cent of the diet.

Its toxicity is reported as about 65 per cent that of sulfapyridine in therapeutic doses. In high dosage it is more toxic than sulfapyridine. When sulfapyridine and sulfathiazole in comparable dosage were given to monkeys and growing rats daily for from two to eight weeks, sulfapyridine was clearly more toxic. The principal pathologic change noted after both drugs in all species was renal damage.

According to Barlow and Homburger,[4] sulfathiazole and sulfamethylthiazole prolonged the life of mice infected experimentally with virulent *Staphylococcus aureus*. It prevented the development and allowed healing of abscesses in the kidneys and other organs in a significant number of mice. Carroll, Kappel, Jones, Gallagher and

1. Fosbinder, R. J.; and Walter, L. A.: Sulfanilamide Derivatives of Heterocyclic Amines. Jour. Amer. Chem. Soc., **61**:2032, 1939.

2. McKee, C. M.; Rake, Geoffrey; Greep, R. O.; and van Dyke, H. B.: Therapeutic Effects of Sulfathiazole and Sulfapyridine. Proc. Soc. Exper. Biol. & Med., **42**:417 (Nov.) 1939.

3. van Dyke, H. B.; Greep, R. O.; Rake, Geoffrey; and McKee, C. M.: Observations on the Toxicology of Sulfathiazole and Sulfapyridine. Ibid., p. 410.

4. Barlow, O. W.; and Homburger, E.: Specific Chemotherapy of Experimental Staphylococcus Infections with Thiazole Derivatives of Sulfanilamide. Ibid., **42**:792 (Dec.) 1939.

DiRocco,[1] in the January number of the SOUTHERN MEDICAL JOURNAL, report survival of *Staphylococcus aureus* infected mice, and of four patients with severe *Staphylococcus aureus* infections, after treatment with sulfamethylthiazole. It is apparently a drug worthy of further investigation. A great many drugs have been presented as active against *Staphylococcus aureus*. A popular one seventeen years ago was mercurochrome.

In evaluating any of the sulfonamide products one has to consider its chemical constitution, its toxicity, and its effect against a specific micro-organism both immediate and late. It was reported in analysis of a recent large series of cases of gonorrhea treated by various measures that sulfapyridine induced a more immediate relief of symptoms than did sulfanilamide, but that late relapses (after six months) were more numerous after the former drug.[2]

The suggestion is noted below that the effectiveness of sulfanilamide *in vivo* against a given species of plasmodium parallels its effect in depressing the metabolism of the micro-organism *in vitro*. Comparative depressing effects of the various new sulfonamide derivatives against strains of staphylococci might provide useful information.

The sulfonamides are undoubtedly the great therapeutic contribution of the decade, and their field of usefulness is far from exhausted. There is still hope that one will appear which will hit a cold in the head.

SULFANILAMIDE IN MALARIA

The sulfonamides are as interesting for their failures as for their striking successes in eradication of infection. Sulfanilamide, according to Coggeshall,[3] of the Rockefeller Institute, is quite active against a fatal acute monkey malaria caused by *Plasmodium knowlesi*, and ineffective in the treatment of a milder chronic monkey malaria caused by *Plasmodium inui*. *P. knowlesi* causes a virulent malaria in humans, as in monkeys. Against certain canary and chicken malarias, sulfanilamide has been shown to be inactive, and, according to Coggleshall, it is a very inferior agent against human malaria.

The sulfonamides are believed to act not directly upon a given parasite, so that the activity or lack of it may be demonstrated *in vitro*, but in some way through the host by stimulating host resistance. For study of its effects, it is necessary to infect and treat living animals. The question arises, does sulfanilamide activity in malaria vary not only according to the species of parasite, but from host to host?

Coggleshall has shown that the fatal *P. knowlesi* monkey infection is eradicated by treatment with a comparatively small amount of sulfanilamide, which completely relieves symptoms in a few days, and so sterilizes the monkey blood that it is no longer capable of transmitting the infection to other monkeys in which its blood is injected; the monkey does not spontaneously relapse, but can be reinfected by reinoculation, a fact usually accepted as proof of cure. If monkeys are infected with the chronic variety of malaria, caused by *Plasmodium inui*, and treated with sulfanilamide, the parasite count of the blood is at first reduced, and the plasmodia gradually disappear from the blood smears for two weeks. After this, they reappear and increase steadily so that six weeks after treatment the parasite count of the treated animal is the same as that of the controls. The effect of sulfanilamide is not detectable.

If the monkeys are infected with both *Plasmodium knowlesi* and *Plasmodium inui*, the fatal and chronic malarias, and are untreated, they die rapidly of *P. knowlesi* infection. If they are treated with sulfanilamide, the drug selectively destroys *P. knowlesi* without affecting *P. inui* and the monkeys cured of *P. knowlesi* show the usual chronic disease characteristic of *P. inui* infection. There is no antagonism between the two parasites; *P. inui is* not hostile to *P. knowlesi* and does not act as a curative agent against it. Activity of a drug depends upon the species of micro-organism, not upon the host.

Coggleshall studied oxygen consumption of the two varieties of plasmodia and found that equal numbers of knowlesi consumed six times as much oxygen as inui. Sulfanilamide *in vitro* had a marked paralyzing effect on the metabolism, or oxygen consumption of *P. knowlesi*, not on *inui*. The effect of sulfanilamide is therefore, he concludes, probably an interference with the metabolism of the parasite; and he confirms

1. Carroll, Grayson; Kappel, Louis; Jones, Lloyd; Gallagher, F. W.; and DiRocco, F. W.: Sulfamethylthiazole: A Report of Its Clinical Use in Staphylococcus Septicemia with Apparent Success. Report of Animal Experiments. Sou. Med. Jour., **33**:83 (Jan.) 1940.

2. Cokkinis, A. J.; and McElligott, G. L. M.: Relapses After Sulfonamide Cure of Gonorrhea. Brit. Med. Jour., No. 4117, p. 1080, 1939.

3. Coggeshall, L. T.: Selective Action of Sulfanilamide on the Parasites of Experimental Malaria in Monkeys *in vivo* and *in vitro*. Jour. Exper. Med., **71**:13 (Jan.) 1940.

other workers to the effect that the influence of an antimalarial drug on the metabolism of a malaria parasite gives the most direct indication of its efficiency as a therapeutic agent. No proposed antimalarial drug, he says, should be discarded on the basis of negative results against one variety of plasmodium, or accepted for all because of activity against one. Very great differences have been demonstrated between the susceptibility of several varieties to a given sulfonamide compound.

Comparison of the metabolism of the various plasmodia in the presence of the several new sulfonamides now coming into prominence will perhaps lead to further developments in malaria therapy.

TWENTY-FIVE YEARS AGO

From Journals of 1915

The Platform of the Southern Medical Association.[1]—In the atrocious carnival of murder now devastating the fairest regions of Europe the final account of the work of each day is reckoned and flashed to mourning nations as so many killed, so many wounded, so many missing. * * * Fortunate America is not at war. * * * The business of eating, drinking, multiplying and dollar-getting proceeds undisturbed, and only an occasional funeral bell reminds us that all must die. * * * Yet here in fortunate America * * * every twenty-four hours fifteen hundred * * * fellow citizens die from avoidable diseases. * * * Every day, without intermission, the year round, Sundays and week days, this army of 1,500 souls is reported missing from the ways that know them, and the causes of their loss are avoidable, and capable of being eliminated or controlled. * * * True, the Agricultural Department conserves the crops that feed us. True, the Public Health Service, though fettered to an alien department, does noble service in prominent places. But * * * we are fed on doctored corn, poisoned meats, rotten goods in pails and cans. We are lied to and stolen from. Epidemics slay our children. State and municipal governments are governed by fear of the voters and give us no relief. We know what we want. We have proclaimed it aloud in numbers and singly. *Give us a Department of Public Health and Sanitation.*

Even Soldiers Should Change Their Underwear.[2]—Within about a couple of months of the troops of the 1st London Division coming into camp under canvas at Crowborough. * * * A certain number of men * * * were experiencing the unpleasant effects incidental to infestation by lice * * * not only at that time had the men not been supplied with a second service suit, but a number of those affected were found not to be in possession of a second shirt or change of underclothing. * * * All the battalion medical officers were called together for the purpose of informing them as to the various aspects of the question, including the life history of the body louse, *Pediculus vestimenti* * * * at the same time commanding officers were communicated with as to the necessity for insuring that all the men under their command should be provided with at least a second shirt and, if possible, a complete change of underclothing.

Ants Instead of Lice.[3]—M. Jousseaume proposed the use of tobacco smoke versus body lice. Another method is to place the clothing infested with these parasites on an ant hill. The ants will make short work of the parasites.

First Aid for Abdominal Wounds.[4]—M. Sencert dealt with treatment of penetrating wounds of the abdomen in ambulances at the front. In view of the impossibility of interfering under satisfactory circumstances and with adequately sterilized material, the author says that one should content oneself with immediate and absolute immobilization, withholding all food. Cure will result in those cases in which a clot obliterates the bleeding vessel or in which adhesion closes a perforated coil of intestine. It is physically impossible for the surgical personnel of the ambulance, when in less than a day the necessary surgical attention has to be given to from 250 to 300 wounded, to devote the greater part of the time to doing a few laparotomies. Out of 66 wounded abdomens that M. Sencert has seen treated in this way, of which it was impossible to follow up 58 completely, 45 died and 13 were cured.

Acetyl Salyclic Acid.[5]—The Board of Trade has made an order regarding the aspirin trade mark, the effect of which is to make the word "aspirin" public property.

1. Editorial. Missing. Sou. Med. Jour., **8**:157 (Feb.) 1915.
2. Copeman, S. Monckton: Note on a Successful Method for the Extermination of Vermin Infesting Troops. Lancet, **188**:273 (Feb. 6) 1915.
3. From our own correspondent, Paris. Lancet, **188**:295 (Feb. 6) 1915.
4. Ibid.
5. Ibid., p. 434.

Book Reviews

Rural Medicine. Proceedings of the Conference Held at Cooperstown, New York, October 7 and 8, 1938. 268 pages. Springfield, Illinois: Charles C. Thomas, 1939. Cloth $3.50.

The Cooperstown Conference shows what a determined group of practitioners can do in analyzing the health problems and potentialities of their community. This conference was organized by the staff of the Mary Imogene Bassett Hospital. The book is divided into four parts. The first deals with the rural morbidity, the economic and social background of the county and the experiences of the staff in caring for these people. The second part is concerned with the health program, the third with postgraduate medical education, and the last with the economics of rural medicine.

After each part has been presented, there is a discussion by outstanding leaders in the fields of medicine, business and public health. While the various phases of the work are limited by being confined to a single county, the contribution achieves importance by being well done, by the frank discussions, and by becoming a part of our knowledge of medical distribution.

Handbook of Skin Diseases. By Leon Hugh Warren, B.A., M.D., M.Sc. (Med.), Acting Assistant Surgeon (Dermatology) in the Office of Dermatoses Investigations of the United States Public Health Service. With a Foreword by Frederick D. Weidman, M.D. 321 pages. New York: Paul B. Hoeber, Inc., 1940. Cloth $3.50.

For a handbook of its size this small volume treats of a surprisingly complete list of affections of the skin. Two things contribute to this. There is the streamlined, "telegraphic" style. The author not only eliminates all facts which he considers non-essential, but also all words which could be omitted without loss of coherence. Then there is the exceptionally complete though concise 45-page section on treatment. Under the various diseases only a few words of indication of the line to be followed need be given and repetition of directions and prescriptions is avoided. The author wisely leaves out anything but the mere mention of x-ray.

The overburdened undergraduate should find in this book all he has time to read and learn in a course for which few hours are allotted. The practicing physician can learn much from it, and the specialist will readily find it a good reminder, a spark to set off an otherwise inactive train of thought, a fuse connecting conscious thought with memories for the moment buried.

Valuable for all is the complete list of synonyms and eponyms, reproduced in the 45 pages of index.

Dr. Colwell's Daily Log for Physicians. A Brief, Simple, Accurate Financial Record for the Physician's Desk. Champaign, Illinois: Colwell Publishing Company, 1939.

The Daily Log is a well arranged, comprehensive and adequate financial record by which the physician can quickly account for each service rendered. It suffices for a bookkeeping system and will be most useful in computing income tax.

The case history cards are also useful.

Psychobiology and Psychiatry: A Textbook of Normal and Abnormal Human Behavior. By Wendell Muncie, M.D., Associate Professor of Psychiatry, Johns Hopkins University. With a Foreword by Adolf Meyer, M.D., LL.D., Sc.D., Henry Phipps Professor of Psychiatry and Director of the Department of Psychiatry, Johns Hopkins University. 739 pages, illustrated. St. Louis: The C. V. Mosby Company, 1939. Cloth $8.00.

This book presents the conceptions, teaching and working methods of the Henry Phipps Psychiatric Clinic at the Johns Hopkins Hospital. It embodies in one volume the psychobiologic psychiatry of Adolph Meyer. He has for many years taught that man is not merely the sum of anatomic and physiologic activities, but an integrated individual within the general framework of biology whose mentally integrated functioning is not a matter of chance, but dependent upon (1) innate equipment, (2) capacity for growth and organization, and (3) the modifying influences of immediate and more remote environment. This thesis is discussed under the headings of psychobiology, the study of normal behavior, abnormal behavior, and treatment. In addition there is presented in outline form the historical background of these concepts. The book is well written and the material is systematically presented.

Fractures. By Paul B. Magnuson, M.D., F.A.C.S., Associate Professor of Surgery, Northwestern University Medical School; Attending Surgeon, Passavant Memorial Hospital and Wesley Memorial Hospital, Chicago. Third Edition. 511 pages, illustrated. Philadelphia: J. B. Lippincott Company, 1939. Cloth $5.00.

The author has made an effort to simplify the methods of treatment and to approach the problem of fractures from the standpoint of anatomy and physiology. The operative treatment for fractures has not been included except to indicate certain procedures which may be used by those who are skilled in this branch of surgery.

Additions have been made in discussion of first aid in the treatment of compound fractures, in the treatment of impacted fractures of the surgical neck of the humerus and in the treatment of fractures of both bones of the forearm by the use of Kirschner wire. Also further information on intracapsular fractures of the neck of the femur has been presented.

This is a useful ready reference to the early treatment of fractures, but not the full discussion which is usually needed by the general surgeon and general practitioner.

Southern Medical News

ALABAMA

The Southeastern Surgical Congress, eleventh annual assembly, will be held in Birmingham, March 11, 12 and 13, at the Tutwiler Hotel. The preliminary program gives the names of thirty-nine outstanding teachers and clinicians, among them Dr. Quitman U. Newell, St. Louis, Missouri, President-Elect of the Southern Medical Association. The President of the Congress is Dr. R. L. Sanders, Memphis, Tennessee; President-Elect, Dr. Irvin Abell, Louisville, Kentucky, a Past-President of the Southern Medical Association; Vice-President, Dr. Grady E. Clay, Atlanta, Georgia; and Secretary-Treasurer, Dr. B. T. Beasley, 701 Hurt Building, Atlanta, Georgia. Chairmen of the Birmingham committees are: Dr. David S. Moore, General Chairman; Dr. Cecil D. Gaston, hotels; Dr. S. G. Stubbins, reception; Dr. R. M. Brannon, transportation; Dr. K. F. Kesmodel, auditorium; Dr. Lee F. Turlington, entertainment; Dr. H. Earle Conwell, scientific; Dr. Chalmers H. Moore, clinic; Dr. Gilbert F. Douglass, publicity; and Mrs. O. P. Board, ladies' entertainment.

Dr. Roy J. Settle, formerly of Inman, South Carolina, has been named Health Officer for Clarke County to succeed Dr. B. S. Black, who has resigned to enter private practice.

Dr. E. T. Norman, Linden, was elected President and re-elected Secretary and Treasurer of the Marengo County Medical Society at the recent meeting in Linden. Dr. Julian P. Howell, Demopolis, was elected Vice-President.

Dr. W. T. Cocke, Demopolis, was recently elected President of the Marengo County Board of Health; Dr. W. E. Allen, Sweetwater, and Dr. T. C. Cameron, Faunsdale, were elected members of the Board.

Dr. D. T. Ramsey, Jr., Akron, has been appointed physician with the Central Iron & Coal Company at Holt as Company Physician. He will also engage in private practice at Holt.

Dr. Lloyd Nolan, Birmingham, was elected a Vice-President of the Frisco System Medical Association at their recent meeting in Tulsa, Oklahoma.

The Coffee County Medical Society has elected the following officers for the coming year: President, Dr. C. P. Hayes, Elba; Vice-President, Dr. W. A. Stanley, Enterprise; Secretary-Treasurer, Dr. W. A. Lewis, Enterprise, re-elected.

DEATHS

Dr. William J. Love, Birmingham, aged 68, died December 11.

Dr. O. C. McCarn, Warrior, aged 62, died January 15.

Dr. Ernest F. Salter, Banks, aged 69, died November 30 of myocarditis and influenza.

Continued on page 38

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You will enjoy owning and using this new 2nd Edition of "Handbook of ORTHOPAEDIC SURGERY," written to satisfy a continued demand for a concise textbook on contemporary orthopaedic surgery. In revising consideration was given the criticisms of orthopaedic surgeons who used the previous edition in teaching, and also the reviews of the original edition.

The book is divided into 24 chapters. Sixteen chapters are devoted to a discussion of the lesions of orthopaedic surgery. Seven chapters are given over to the lesions of various regions of the body. The book is well planned, easy to read and understand. Fundamental facts and principles are given very concisely. The book embraces the entire gamut of diseases, deformities, and injuries commonly accepted as falling within the domain of orthopaedic surgery, both mechanical and operative. Throughout, the author has stressed the importance of physiological and anatomical considerations in determining diagnosis and treatment.

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Continued from page 228

ARKANSAS

The Jefferson County Medical Society has elected the following officers for the coming year: President, Dr. H. T. Capel; Vice-President, Dr. B. D. Luck, Jr.; Secretary-Treasurer, Dr. T. J. Cunningham, Jr., all of Pine Bluff.

The Bradley County Medical Society has elected the following officers for the coming year: President, Dr. W. B. Reasons, Hermitage; Vice-President, Dr. Rufus Martin, Warren; Secretary-Treasurer, Dr. W. J. Hunt, Warren.

The Sevier County Medical Society has elected the following officers for the coming year: President, Dr. G. L. Kimball; Vice-President, Dr. C. A. Archer; Secretary-Treasurer, Dr. J. S. Hendricks, all of DeQueen.

The Franklin County Medical Society has elected the following officers for the coming year: President, Dr. W. H. Gibbons, Ozark; Vice-President, Dr. E. W. Pillstrom, Coal Hill; Secretary-Treasurer, Dr. Thos. Douglass, Ozark.

The Union County Medical Society has elected the following officers for the coming year: President, Dr. H. J. Mayfield; Vice-President, Dr. J. B. Wharton, Jr.; Secretary-Treasurer, Dr. J. W. Harper, all of El Dorado.

The Ouachita County Medical Society has elected the following officers for the coming year: President, Dr. C. S. Early; Vice-President, Dr. R. H. Whitehead, Jr.; Secretary, Dr. R. B. Robins, all of Camden.

The Independence County Medical Society has elected the following officers for the coming year: President, Dr. F. Q. Wyatt; Vice-President, Dr. C. A. Churchill; Secretary-Treasurer, Dr. J. J. Monfort, all of Batesville.

The Little River County Medical Society has elected the following officers for the coming year: President, Dr. P. H. Phillips; Vice-President, Dr. E. R. King; Secretary-Treasurer, Dr. J. W. Ringgold, all of Ashdown.

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Interviews regarding the American Board examinations will be given by members of the American Board of Ophthalmology to those registered for Course II.

For further details of above courses apply to the Secretary, Miss Louisa G. Wells, 927 17th Street, N.W., Washington, D. C.

The Lawrence County Medical Society has elected the following officers for the coming year: President, Dr. J. F. Jackson, Walnut Ridge; Vice-President, Dr. T. Z. Johnson, Walnut Ridge; Secretary-Treasurer, Dr. T. C. Guthrie, Smithville.

The Garland County Medical Society has elected the following officers for the coming year: President, Dr. C. H. Lutterloh; Vice-President, Dr. Foster Jarrell; Secretary-Treasurer, Dr. W. E. Gray, all of Hot Springs National Park.

The Sebastian County Medical Society has elected the following officers for the coming year: President, Dr. H. C. Dorsey; Vice-President, Dr. T. P. Foltz; Secretary, Dr. Ralph E. Weddington; Treasurer, Dr. W. R. Brooksher, all of Fort Smith.

The Pulaski County Medical Society has elected the following officers for the coming year: President, Dr. H. W. Hundling; Vice-President, Dr. G. W. Reagan; Secretary, Dr. E. H. White; Treasurer, Dr. R. J. Calcote, all of Little Rock.

The Mississippi County Medical Society has elected the following officers for the coming year: President, Dr. L. L. Hubener; Vice-President, Dr. J. E. Beasley; Secretary-Treasurer, Dr. F. D. Smith, re-elected, all of Blytheville.

The Cross County Medical Society has elected the following officers for the coming year: President, Dr. Ruffin Longest; Vice-President, Dr. Thos. G. Price; Secretary-Treasurer, Dr. Thomas A. Peterson, all of Wynne.

Dr. Fred H. Krock, Fort Smith, has been elected Chief of Staff of Sparks Memorial Hospital.

Dr. E. W. Wood, Marshall, has been elected President of the Blueback Spellers' Society.

Dr. Cyril Lewis Hyatt, Little Rock, and Miss Wanda White, Van Buren, were married November 5.

DEATHS

Dr. William Franklin Akin, Branch, aged 65, died November 13.

Dr. Lee Vallette Parmley, Little Rock, aged 47, died December 27.

Dr. Joseph J. Stewart, Lamar, aged 83, died October 15.

Dr. Wiley S. May, Little Rock, aged 68, died November 3.

Dr. Francis Owington Rogers, Little Rock, aged 63, died November 8.

Dr. William Thomas Rowland, Arkadelphia, aged 69, died November 26.

Dr. Edward Karl Allis, North Little Rock, aged 58, died November 25.

Dr. William C. Haltom, Jonesboro, aged 70, died November 19 of mitral regurgitation and chronic nephritis.

DISTRICT OF COLUMBIA

Dr. George M. Leiby, formerly Director of the Division of Venereal Disease Control of the North Carolina State Department of Health, with headquarters at Raleigh, has been appointed the first full-time Director of the Venereal Disease Service for the District of Columbia.

Washington's new morgue has recently been completed on the grounds of Gallinger Hospital, and at the dedicatory ceremonies Dr. Andrew Magruder MacDonald, Coroner, in an address outlined the increased work since the unit was established in 1868.

The Georgetown University Alumni Club has elected the following officers for the coming year: President, Dr. Leo Brison Norris; Vice-President, Dr. Aloysius J. Connolly; Secretary-Treasurer, Dr. Harry F. Davies, all of Washington.

The St. Elizabeths Hospital Medical Society has elected the following officers for the coming year: President, Dr. W. W. Eldridge; Secretary-Treasurer, Dr. M. B. Pettit, both of Washington.

Dr. Wallace M. Yater, Washington, has been elected a member of the Advisory Board of the Alumni Association of the Mayo Foundation for a period of three years.

DEATHS

Dr. Robert Cooke Bicknell, Washington, aged 77, died November 16 of arteriosclerotic heart disease.

Dr. C. Augustus Simpson, Washington, aged 57, died December 9 of heart disease.

FLORIDA

Dr. William H. Ball, Panama City, has been appointed State Director of Maternal and Child Health with headquarters in Jacksonville. Dr. Dea C. Witt, formerly of Jacksonville, will replace Dr. Ball as Director of the Bay County Health Unit.

The Florida Public Health Association recently elected the following officers for the coming year: President, Dr. Albert B. McCreary, Jacksonville; Vice-Presidents, Dr. Leander J. Graves,

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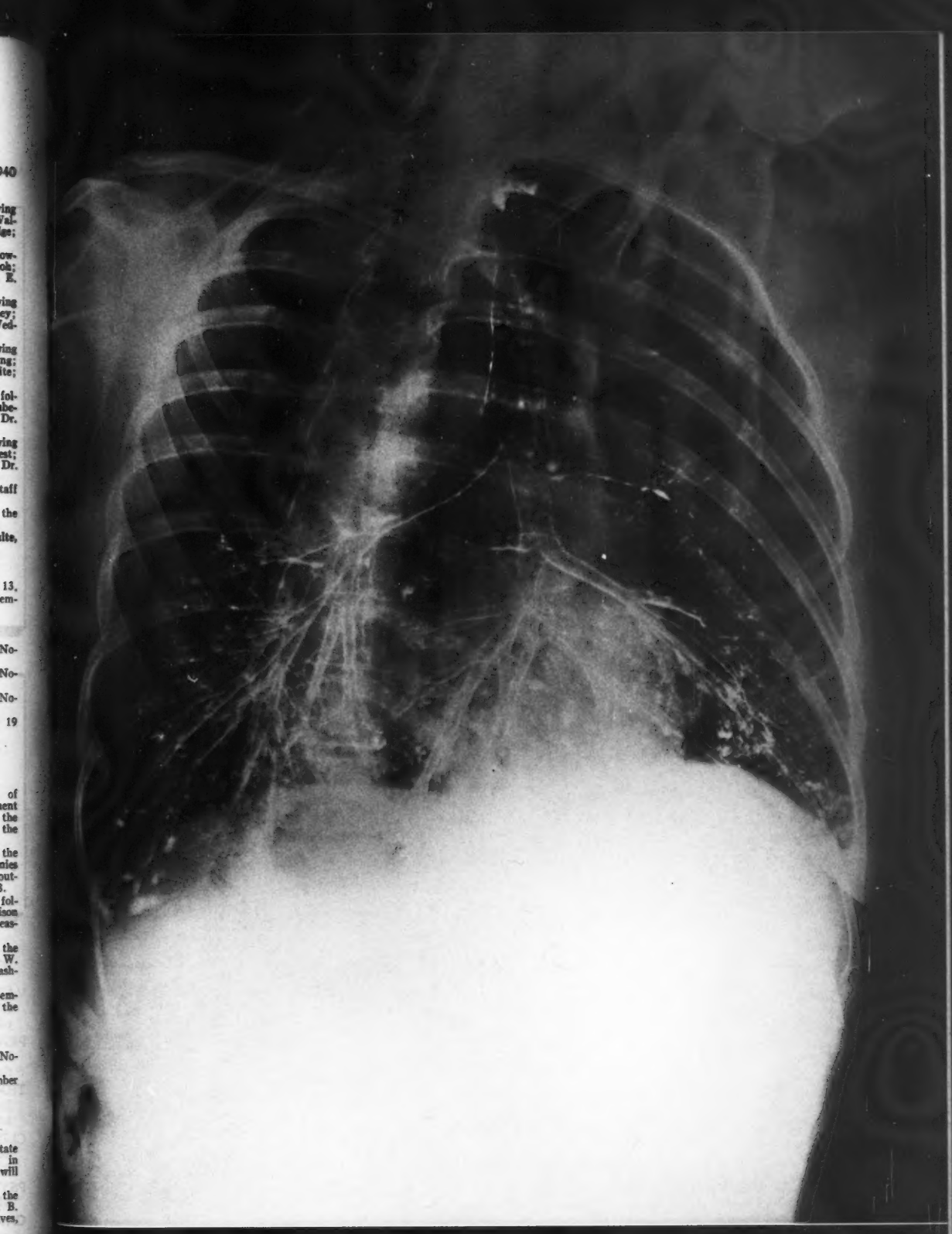

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(*See back of this page*)

Excerpt from the Medical Literature . . . .

"The only method by which the presence of bronchiectasis can be accurately established is x-ray visualization of the dilated bronchi. The introduction of lipiodol for the purpose of mapping the bronchial tree by Sicard and Forestier created a new era in the diagnosis of bronchiectasis. For although symptoms, physical signs, and ordinary x-ray examination are often suggestive, a positive diagnosis cannot be made unless one can actually see the images of the dilated bronchi. . . . It is essential that both lungs be mapped.

• • •

"It is well to include the nasal sinuses in the examination of every patient with bronchiectasis. It is now well recognized that there is a lymphatic connection between the upper and lower respiratory tracts."

—S. Clin. North America, *18*:1191-4, October, 1938

The obvious excellence of the original radiograph reproduced on the reverse side of this page is due, first, to the knowledge of the radiologist; second, to the inherent qualities of Eastman Ultra-Speed X-ray Film.

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(*See reverse side of this page*)

Continued from page 38

Tallahassee, and Dr. A. C. Newman, Jacksonville; Secretary-Treasurer, Dr. Edward M. L'Engle, Jacksonville.

Dr. George S. McClellan, Pompano, and Dr. Isaac W. Chandler, Avon Park, were both appointed members of the State Board of Medical Examiners.

Dr. R. Marshall Faver, Miami, did postgraduate work in ophthalmology at the Chicago Eye, Ear, Nose and Throat College recently.

DEATHS

Dr. Albert G. H. Holmes, Miami Beach, aged 75, died October 30 of coronary occlusion.

Dr. Roy John Boynton, Miami, aged 58, died October 21 of cerebral hemorrhage and hypertension.

Dr. Willis Adam Turnbull, Tampa, aged 71, died October 23.

Dr. Corbett Edward Tumlin, Miami, aged 46, died November 6.

Dr. Sarah Shomer, Miami, aged 43, died October 7 of septicemia.

GEORGIA

A grant by the Joseph B. Whitehead Foundation has made possible the J. B. Whitehead Chair of Surgery at Emory University School of Medicine, Atlanta.

The Georgia Industrial Surgeons' Association recently elected the following officers for the coming year: President, Dr. Robert L. Rhodes, Augusta; Vice-President, Dr. Richard E. Newberry, Atlanta; Secretary-Treasurer, Dr. John W. Simmons, Brunswick.

Dr. V. P. Sydenstricker, Professor of Medicine at the University of Georgia School of Medicine, Augusta, has recently been awarded a grant of $6,000 by the Markle Foundation for the continuation of his studies on pellagra.

Dr. John L. Elliott, Savannah, has been elected President of the Georgia Tuberculosis Association.

The following Georgia physicians were recently elected to fellowship in the American College of Surgeons: Dr. E. C. Herman, LaGrange; Dr. J. S. Holder, LaGrange; Dr. J. B. Avera, Brunswick; Dr. Carl C. Garver, Atlanta; Dr. O. D. Gilliam, Colum-

Continued on page 40

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Review Courses in medicine, in surgery and in gynecology and obstetrics begin January 8, 1940, and continue through March 30, 1940. Three courses of four weeks each are offered in each branch.

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A special course in gynecological surgery will be offered beginning January 8, 1940.

A special course in otolaryngology (anatomy, histology, pathology, etc.), lasting six weeks, will begin March 11, 1940.

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Continued from page 39

bus; Dr. Willard R. Golsan, Macon; Dr. Paul H. Milton, Fort Oglethorpe; Dr. Robert L. Oliver, Savannah; and Dr. F. B. Rawlings, Sandersville.

Dr. Hugh S. Edward, Atlanta, and Miss Kathleen A. Williams, Holden, Massachusetts, were married December 9.

DEATHS

Dr. Stephen R. Mitchell, Pineview, aged 84, died November 5 of heart disease.

Dr. Thomas J. Collins, Griffin, aged 89, died October 26 of senility.

KENTUCKY

DEATHS

Dr. Christopher C. Threlkel, Morgantown, aged 66, died November 9.

Dr. John H. Metcalfe, Louisville, aged 74, died November 27 of arteriosclerotic heart disease.

LOUISIANA

The New Orleans Graduate Medical Assembly will hold its fourth annual assembly at the Roosevelt Hotel, February 26-29, honoring Dr. Rudolph Matas, Emeritus Professor of General and Clinical Surgery, Tulane University School of Medicine. Dr. Matas, nationally and internationally known for his work in the field of vascular surgery, will be given a reception on the opening night of the assembly as a tribute to his sixtieth year in active practice. The registration fee of $10.00 covers all clinics, daily round table luncheons, and the entertainment.

The Orleans Parish Medical Society has elected the following officers for the coming year: President, Dr. Gilbert C. Anderson; First Vice-President, Dr. Edmund L. Leckert; Second Vice-President, Dr. Andrew V. Friedrichs; Third Vice-President, Dr. Daniel J. Murphy; Secretary, Dr. Edwin L. Zander; and Treasurer, Dr. Edwin H. Lawson, all of New Orleans.

Dr. Jules Myron Davidson, New Orleans, has been received into the Fellowship of the American College of Chest Physicians.

Dr. Marion Souchon, New Orleans, is exhibiting a painting at the Julien Levy Gallery in New York City, which has been well received.

The Bi-Parish Medical Society has elected the following officers for the coming year: President, Dr. C. S. Miller, Jackson; Vice-President, Dr. A. D. Long, Jackson; Secretary-Treasurer, Dr. E. M. Toler, Clinton.

The DeSoto Parish Medical Society has elected the following officers for the coming year: President, Dr. W. B. Hewitt; Vice-President, Dr. R. P. Thaxton; Secretary-Treasurer, Dr. R. A. Tharp, all of Mansfield.

The Ouachita Parish Medical Society has elected the following officers for the coming year: President, Dr. D. T. Milam; Vice-President, Dr. H. E. Guerriero; Secretary-Treasurer, Dr. L. L. Titche, all of Monroe.

The Third District Medical Society has elected the following officers for the coming year: President, Dr. R. S. Hernandez, Duson; Vice-President, Dr. L. M. Villien, Jeanerette; Secretary-Treasurer, Dr. J. J. Burdin, Lafayette.

The Avoyelles Parish Medical Society has elected the following officers for the coming year: President, Dr. Philip Jeansonne, Plaucheville; Vice-President, Dr. L. A. Morrogh, Marksville; Secretary-Treasurer, Dr. K. A. Roy, Mansura.

The Iberia Parish Medical Society has elected the following officers for the coming year: President, Dr. J. N. Pharr, New Iberia; Vice-President, Dr. E. T. Duncan, Weeks Island; Secretary-Treasurer, Dr. C. L. Mengis, New Iberia.

The Plaquemine Parish Medical Society has elected the following officers for the coming year: President, Dr. B. H. Carlton, Port Sulphur; Vice-President, Dr. C. M. Johnson, Buras; Secretary-Treasurer, Dr. J. T. Reeves, Buras.

The Rapides Parish Medical Society has elected the following officers for the coming year: President, Dr. N. T. Simmonds; First Vice-President, Dr. J. A. White, Jr.; Second Vice-President, Dr. C. P. Herrington; Secretary-Treasurer, Dr. E. G. Cailleteau, all of Alexandria.

The Red River Parish Medical Society has elected the following officers for the coming year: President, Dr. W. W. Gahagan, Coushatta; Vice-President, Dr. L. S. Huckabay, Harman; Secretary-Treasurer, Dr. F. E. DePriest, Coushatta.

Continued on page 42

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Philadelphia, Penn.
Dr. Frederick H. Falls—Obstetrics
Chicago, Ill.
Dr. Henry B. Orton—Otolaryngology
Newark, N. J.

Dr. Albert D. Kaiser—Pediatrics
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Dr. George G. Smith—Urology
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Dr. Ralph M. Tyson—Pediatrics
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Dr. D. T. Vail, Jr.—Ophthalmology
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Dr. Henry W. Cave—Surgery
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Dr. Henry M. Goodyear—Otolaryngology
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Madison, Wis.
Dr. F. G. Blake—Medicine
New Haven, Conn.
Dr. Reginald Fitz—Medicine
Boston, Mass.
Dr. Maurice B. Visscher—Physiology
Minneapolis, Minn.
Dr. Roy W. Scott—Medicine
Cleveland, Ohio

Programs will be mailed February 1st. Write for one if you do not receive yours.

DR. A. F. COOPER, Secretary-Treasurer

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Continued from page 40

The Sabine Parish Medical Society has elected the following officers for the coming year: President, Dr. S. F. Fraser, Many; Vice-President, Dr. O. L. Sanders, Converse; Secretary-Treasurer, Dr. G. F. Weber, Many.

The Terrebonne Parish Medical Society has elected the following officers for the coming year: President, Dr. S. E. Ellender; Vice-President, Dr. S. C. Collins; Secretary-Treasurer, Dr. W. A. Ellender, all of Houma.

The Webster Parish Medical Society has elected the following officers for the coming year: President, Dr. S. J. Feducia, Cotton Valley; Vice-President, Dr. Byron L. Cook, Minden; Secretary-Treasurer, Dr. B. A. Norman, Minden.

The Fourth District Medical Society has elected the following officers for the coming year: President, Dr. C. R. Gowen; Vice-President, Dr. W. H. Browning; Secretary, Dr. N. J. Bender, all of Shreveport.

Dr. William K. Evans, Lake Providence, has recently been appointed Health Officer of West Carroll Parish.

Deaths

Dr. Avery C. Wilkins, Shreveport, aged 68, died October 26 of malignancy of the biliary tract.

Dr. Jacob Ambrose Storck, New Orleans, aged 73, died November 16.

Dr. Francis Oliver Darby, Baton Rouge, aged 61, died November 12 of coronary occlusion.

Dr. Amedee B. Granger, New Orleans, aged 60, died December 15 as a result of coronary thrombosis.

Dr. Joseph N. Roussel, New Orleans, aged 68, died December 15 of coronary occlusion.

Dr. David L. Watson, New Orleans, aged 61, died December 18 as the result of a fall down the stairs of his home.

MARYLAND

Dr. Raymond Hussey, Dr. Nathan B. Herman and Dr. John W. Pierson, all of Baltimore, have been appointed by the Governor to the State Medical Board for Occupational Diseases. This Board was created in accordance with the new State occupational disease law which regulates compensation in this field.

Deaths

Dr. Wilbur Martin Pearce, Baltimore, aged 72, died October 5 of carcinoma of the right lung.

Dr. Edward Conway Maphis, Mardela Springs, aged 41, died November 15 of an overdose of sleeping potion.

MISSISSIPPI

Dr. Felix J. Underwood, Executive Officer, State Board of Health, Jackson, has announced that the following Mississippi physicians have been awarded postgraduate fellowships for three months' study at Tulane University, New Orleans, Louisiana, these fellowships being granted by the Commonwealth Fund of New York: Dr. Thomas J. Barkley, Isola; Dr. Eugene V. Bramlett, Oxford; Dr. W. L. Chambers, Pickens; Dr. Hiram B. Gilmer, Hickory; Dr. D. L. Hollis, Biloxi; Dr. Robert P. Hudson, Utica; Dr. Charles F. Lacey, Thomastown; and Dr. Hiram C. Sheffield, Jackson.

Dr. David S. Pankratz, formerly connected with the University of Tennessee School of Medicine, Memphis, is now Professor of Gross Anatomy at the University of Mississippi School of Medicine, replacing Dr. A. R. Buchanan, who resigned to assume a similar position with the University of Colorado School of Medicine.

The Clarksdale and Six Counties Medical Society has elected the following officers for the coming year: President, Dr. L. H. Brevard, Deeson; Vice-President, Dr. T. M. Dye, Clarksdale; Secretary-Treasurer, Dr. J. L. Levy, Clarksdale.

The Coast Counties Medical Society has elected the following officers for the coming year: President, Dr. B. B. O'Mara, Biloxi; Vice-Presidents, Dr. A. C. Hewes, Gulfport, Dr. F. O. Schmidt, Ocean Springs, Dr. S. E. Dunlap, Wiggins, and Dr. C. M. Shipp, Bay St. Louis; Secretary-Treasurer, Dr. D. L. Hollis, Biloxi.

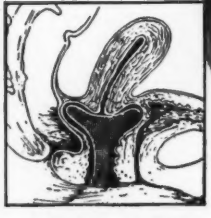
The Newton County Medical Society has elected the following officers for the coming year: President, Dr. Z. T. Hagan, Union; Secretary, Dr. Dudley Stennis, Newton.

The South Mississippi Medical Society has elected the following officers for the coming year: President, Dr. B. T. Robinson,

Continued on page 44

Over 30,000 Sold in the Past Five Years!

The Boilable Gellhorn Pessary



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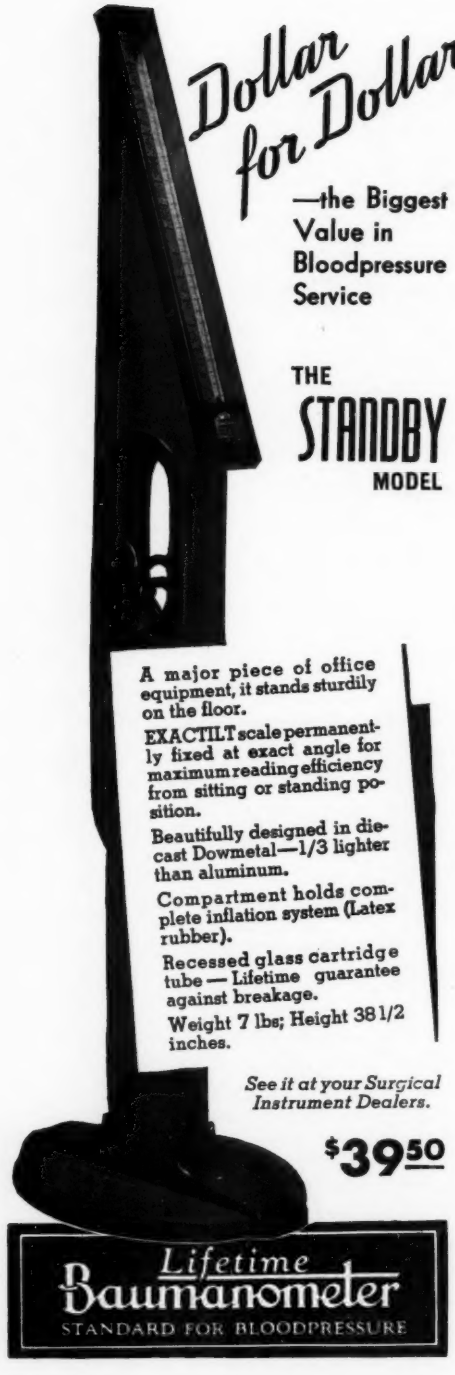
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Continued from page 42

New Augusta; First Vice-President, Dr. H. C. McLeod, Hattiesburg; Second Vice-President, Dr. V. B. Martin, Picayune; Secretary-Treasurer, Dr. V. C. Tampel, Hattiesburg.

Deaths

Dr. Robert L. Casburn, Sumner, aged 82, died October 3 of uremia, hypertrophy of the prostate and chronic myocarditis.

Dr. William Sharp Cranford, Taylorsville, aged 68, died October 31 of staphylococcic septicemia of the left leg.

Dr. J. Milton Terry, Philadelphia, aged 66, died November 15.

Dr. L. A. Barnett, Greenwood, aged 53, died December 5 of a heart attack.

Dr. Tandy B. Harris, Charleston, aged 77, died December 31.

MISSOURI

Dr. Walter Baumgarten, St. Louis, has been elected Editor of the *Journal of the Missouri State Medical Association* to succeed Dr. Edward J. Goodwin, who has been elected Secretary-Editor Emeritus.

Dr. Louis H. Hempelmann, St. Louis, was recently honored at a dinner commemorating the fiftieth anniversary of the Deaconness Hospital. Dr. Hempelmann, the oldest staff member in years of service, was given a watch.

The following doctors who have served on the faculty of St. Louis University School of Medicine for twenty-five years were honored recently at a dinner sponsored by the Women's Club of the School of Medicine: Dr. Theodore Greiner, Dr. Joseph Grindon, Sr., Dr. Andrew C. Henske, Dr. H. H. Kramolowsky, Dr. Albert Kuntz, Dr. James F. McFadden, Dr. Fritz Neuhoff, Dr. Claude D. Pickrell, Dr. M. J. Pulliam, Dr. A. J. Raemdonck, Dr. Phil H. Scherer, Dr. E. T. Senseney, Dr. S. A. Weintraub, Dr. William Weiss, Dr. John Zahorsky, Dr. E. F. McCarthy, and Dr. T. Wistar White.

A dedication ceremony was held November 13, 1939, changing the name of the Rolla Hospital to the Nelle McFarland Memorial Hospital. This was a change in the name only, no change in management or staff being made.

The Atchison-Gentry-Nodaway-Worth Counties Medical Society has elected the following officers for the coming year: President, Dr. Clifton M. Waugh, Tarkio; Vice-President, Dr. Samuel E. Simpson, Stanberry; Secretary-Treasurer, Dr. Charles D. Humberd, Barnard.

The Grundy-Daviess Counties Medical Society has elected the following officers for the coming year: President, Dr. Robert V. Thompson, Jamesport; Vice-President, Dr. William A. Fuson, Trenton; Secretary-Treasurer, Dr. Edgar A. Duffy, Trenton.

The Chariton County Medical Society has elected the following officers for the coming year: President, Dr. Charles D.

Continued on page 46

Classified Advertisements

RATES for insertion in the Classified Column are as follows: $2.00 minimum, which includes the first 50 words; for each word in addition to the original 50 words, the charge is 3c.

WANTED—Assistantship or junior partnership with older physician doing general practice and surgery; F.A.C.S. preferable, but not essential. 30, Jewish, Class A American M.D.; 3 years' hospital experience, large part traumatic surgery. Excellent references. Write Dept. D-64, care JOURNAL.

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THE VALUE of irradiated evaporated milk as a prophylactic source of vitamin D is indicated by the comprehensive study quoted above. Physicians are invited to write for reprints of this article; also for book, "Simplified Infant Feeding," an authoritative discussion of the use of Irradiated Carnation Milk in normal and difficult feeding cases. . . . *Carnation Company, Milwaukee, Wis., Toronto, Ontario, Canada.*

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Continued from page 44

Stratton, Rothville; Vice-President, Dr. Andrew L. Lewis, Sumner; Secretary-Treasurer, Dr. George W. Hawkins, Salisbury.

The Boone County Medical Society has elected the following officers for the coming year: President, Dr. Frank E. Dexheimer; Vice-President, Dr. Karl D. Dietrich; Secretary-Treasurer, Dr. Maurice E. Cooper, all of Columbia.

The Cape Girardeau County Medical Society has elected the following officers for the coming year: President, Dr. C. T. Herbert; Vice-President, Dr. F. W. Hall; Secretary, Dr. C. A. W. Zimmermann; Treasurer, Dr. M. H. Shelby, all of Cape Girardeau.

The Howard County Medical Society re-elected last year's officers: President, Dr. W. B. Kitchen, Glasgow; Secretary, Dr. W. J. Shaw, Fayette.

The Pettis County Medical Society has elected the following officers for the coming year: President, Dr. Archie L. Walter; Vice-President, Dr. Frank B. Long; Treasurer, Dr. Alfred E. Monroe; Secretary, Dr. Charles H. Brady, all of Sedalia.

Deaths

Dr. John Edwin Musgrave, Excelsior Springs, aged 61, died October 28.

Dr. Rufus Charles Harris, St. Louis, aged 63, died October 10.

Dr. Roy Ulysses Stevens, Kansas City, aged 48, died October 30 of carbon monoxide poisoning.

Dr. Jacob Meyer Epstein, St. Louis, aged 67, died November 22 of arteriosclerosis and heart disease.

Dr. Daniel R. Hill, Joplin, aged 74, died November 28 of heart disease.

Dr. Benjamin Thomas Smith, Newburg, aged 76, was killed November 20 in an automobile accident.

Dr. Frank Henry Raab, Kansas City, aged 52, died November 15 of coronary thrombosis.

Dr. Otto L. Rohlfing, St. Louis, aged 64, died November 14 of chronic myocarditis and hypertension.

Dr. Eugene Brezany, St. Louis, aged 68, died November 16 of myocarditis.

Dr. Edward Hugo Shields, St. Louis, aged 73, died November 11 of heart disease.

NORTH CAROLINA

Dr. Thomas F. Vestal, formerly of Worcester, Massachusetts, has recently been appointed Medical Director of the Division of Industrial Hygiene of the North Carolina State Board of Health.

Dr. Lester C. Todd, Charlotte, was elected President of the North Carolina Pathological Society at the recent meeting of the Society in Winston-Salem.

Dr. J. O. Fitzgerald, Jr., Richmond, has been elected President of the Richmond Camera Club.

Dr. J. O. McClelland, Maxton, has been elected the new President of the Seaboard Air Line Railway Surgeons.

The Seventh District Medical Society has elected the following officers for the coming year: President, Dr. C. F. Glenn, Rutherfordton; Vice-President, Dr. N. B. Lubchenko, Harrisburg; Secretary-Treasurer, Dr. H. C. Thompson, Shelby.

The Mecklenburg County Medical Society has elected the following officers for the coming year: President, Dr. Robert Thrift Ferguson; First Vice-President, Dr. T. C. Bost; Second Vice-President, Dr. Andrew Blair; Secretary-Treasurer, Dr. Thomas Baker, all of Charlotte.

Dr. Frederick Da Costa Austin, Jr., Charlotte, and Miss Elizabeth Howard, Guquay Springs, were married November 15, 1939.

Dr. William Dempsey Farmers, Durham, and Miss Elizabeth Sellars, Burlington, were married in November, 1939.

Dr. Frederick Thorns Craven, Concord, and Miss Martha Louise Kindel, Raleigh, were married November 22, 1939.

Deaths

Dr. Herbert Wilcox Knight, Bostic, aged 66, died November 4 of chronic myocarditis.

Dr. John M. Allhands, Cliffside, aged 71, died November 19 of chronic myocarditis and hemiplegia.

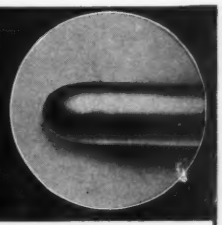
Dr. Sydney Allen Lowry, Kings Mountain, aged 75, died November 6 of enterocolitis and chronic duodenal ulcer.

Dr. Thomas Reid Mellard, Asheville, aged 42, died November 8 of pulmonary tuberculosis.

Dr. Rupert LeRoy Savage, Rocky Mount, aged 65, died November 15 of coronary thrombosis.

Continued on page 48

RADON SEEDS



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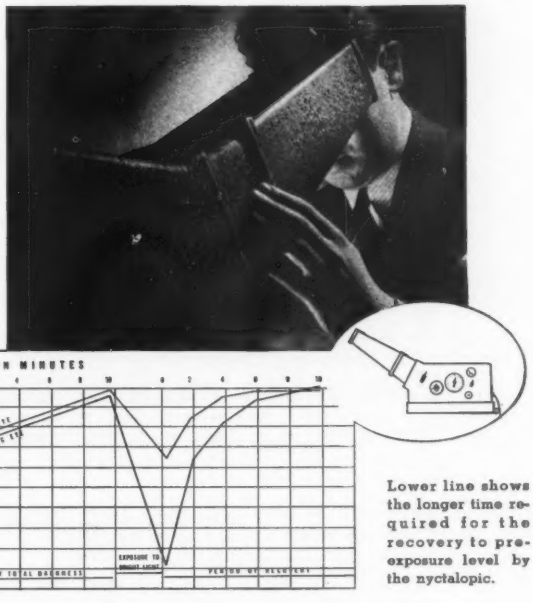
STUDIES IN THE AVITAMINOSES

This page is the second of a series on vitamin deficiencies presented by the research division of The Upjohn Company because of the profession's widespread interest in the subject. A two-page insert on the same subject appears in the February 17 issue of The Journal of the American Medical Association.

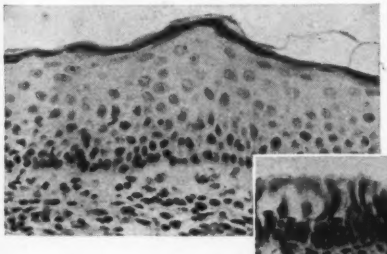
Manifestations of Vitamin A Deficiency

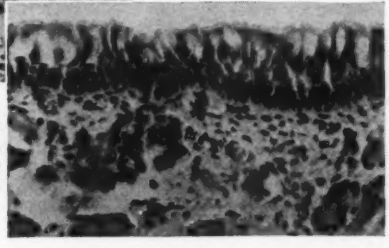
One of the early manifestations of vitamin A deficiency is nyctalopia, a loss of visual acuity in dim light. While several pathologic states (retinitis pigmentosa, toxic amblyopia, detachment of the retina) also produce night blindness, vitamin A deficiency is probably the most frequent cause. After exposure to the blinding glare of a bright light the normal eye adapts itself relatively quickly to lowered illumination. In nyctalopia due to vitamin A deficiency, the time required for recovery of visual acuity is longer.

In otherwise normal eyes, measurement of capacity for dark adaptation by means of the biophotometer has been suggested as a method of discovering vitamin A deficiency.



Lower line shows the longer time required for the recovery to pre-exposure level by the nyctalopic.





Above, stratified, keratinizing epithelium of the turbinate mucous membrane of a vitamin A deficient monkey; at right, normal mucosa.

Pathologic epithelial changes produced by vitamin A deficiency are illustrated by the photomicrographs of turbinate mucous membrane taken from normal and vitamin A deficient monkeys. The progressive pathologic process consists of atrophy of the epithelium, reparative proliferation of the basal cells and finally, as depicted in the upper photograph, replacement of the normal by a stratified, keratinizing epithelium.

UPJOHN

Continued from page 46

Dr. Magnus Eli Conaway, Monroe, aged 71, died November 4 of chronic myocarditis.

Dr. Tilon Vance Moore, Delco, aged 62, died November 14 of coronary thrombosis.

Dr. Manly Blevins, Warrensville, aged 80, died December 9.

OKLAHOMA

The Woods County Medical Society has elected the following officers for the coming year: President, Dr. Theodore D. Benjegerdes, Beaver; Vice-President, Dr. Charles A. Royer, Alva; Secretary, Dr. Oscar E. Templin, Alva.

Physicians receiving the Commonwealth Fellowships for postgraduate work at Tulane University, New Orleans, Louisiana, are: Dr. William G. Dunnington, Cherokee; Dr. Ishmael F. Stephenson, Alva; Dr. Malcolm E. Phelps, El Reno; Dr. Wendell L. Smith, Drumright; Dr. Hugh H. Monroe, Lindsay; Dr. Clella M. Hodgson, Kingfisher; Dr. Battey B. Coker, Durant; and Dr. George K. Hemphill, Pawhuska.

Dr. David W. Gillick, Shawnee, has been appointed Medical Director for District No. 5 of the Indian Medical Service, succeeding the late Dr. Walter S. Stevens. Dr. Gillick's territory includes all of Oklahoma, Kansas, Mississippi, North Carolina and Florida with offices in Oklahoma City.

Dr. Raymond George Jacobs and Miss Mildred Loomis, both of Enid, were married November 4, 1939.

Deaths

Dr. George N. Bilby, Alva, aged 71, died November 26 of mixed cell sarcoma.

Dr. Micajah Haynes, Vinita, aged 88, died October 29 of cerebral arteriosclerosis.

Dr. T. O. Crawford, Dewey, aged 66, died October 20.

SOUTH CAROLINA

The Columbia Medical Society has elected the following officers for the coming year: President, Dr. Alfred F. Burnside; Vice-President, Dr. M. Whitfield Cheatham; Secretary, Dr. James T. Quattlebaum; Treasurer, Dr. W. A. Hart, all of Columbia.

The Aiken County Medical Society has elected the following officers for the coming year: President, Dr. W. A. Whitlock, Jr.; Vice-President, Dr. Huger T. Hall; Secretary-Treasurer, Dr. R. H. Wilds, all of Aiken.

The Fifth District Medical Society has elected the following officers for the coming year: President, Dr. R. L. Crawford; Vice-President, Dr. R. C. Brown; Secretary-Treasurer, Dr. J. C. Harris, all of Lancaster.

The Pee Dee Medical Society has elected the following officers for the coming year: President, Dr. Julian P. Price, Florence; Vice-Presidents, Dr. R. M. Newsome, Ruby, Dr. McIver Willcox, Darlington, Dr. William Bethea, Latta, Dr. E. M. Hicks, Florence, Dr. E. M. Dibble, Marion, Dr. Curtis Hunsucker, Bennettsville, and Dr. J. W. Varner, Conway; Secretary-Treasurer, Dr. Robert Stith, Florence, re-elected.

Dr. James Wilkinson Jervey and Mrs. Maude Earle Hammond Lewis, both of Greenville, were married in October, 1939.

Deaths

Dr. George P. Neel, Greenwood, aged 73, died December 3.

TENNESSEE

The Mid-South Postgraduate Medical Assembly, fifty-fifth annual session, will be held at Memphis, February 13, 14, 15 and 16, at the Peabody Hotel. There will be clinical sessions with presentations by twenty-four outstanding clinicians and teachers with round table luncheons. Dr. H. Fay H. Jones, Little Rock, Arkansas, is President; Dr. J. L. Dunavant, Ripley, Tennessee, is President-Elect, and Dr. A. F. Cooper, Goodwin Institute Building, Memphis, is Secretary.

The Memphis and Shelby County Medical Society has elected the following officers for the coming year: President-Elect, Dr. E. D. Mitchell, Sr.; President, Dr. William Calvert Chaney; Vice-President, Dr. C. E. Warde; Secretary, Dr. A. F. Cooper, re-elected; Treasurer, Dr. E. G. Kelly, re-elected, all of Memphis.

Continued on page 50

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Continued from page 48

The Five-County Medical Society has elected the following officers for the coming year: President, Dr. J. V. Hughes, Savannah; Vice-Presidents, Dr. S. L. Stephenson, Savannah, Dr. J. T. Keeton, Clifton, Dr. J. W. Danley, Lawrenceburg, Dr. W. E. Boyce, Flatwoods, and Dr. O. A. Kirk, Linden; Secretary-Treasurer, Dr. Dexter L. Woods, Waynesboro.

The Smith County Medical Society has elected the following officers for the coming year: President, Dr. Lillard Sloan, Carthage; Vice-President, Dr. R. E. Garrett, Dixon Springs; Secretary-Treasurer, Dr. Thayer S. Wilson, Gordonsville.

Dr. Chas. C. Smeltzer, Knoxville, announces the opening of offices at 605 Walnut Street for the practice of surgery and medicine.

Dr. H. H. Hudson has removed from Murfreesboro to Dyersburg.

Dr. W. E. Turner has removed from Lobelville to Piggott, Arkansas.

Dr. Dennis B. Fox, Nashville, and Miss Dora Helen Jones, Jonesboro, were married December 15.

Deaths

Dr. Clinton Hill Morgan, Knoxville, aged 64, died November 11.

Dr. William Richard Orr, Bryant Station, aged 78, died November 3 of myocarditis.

Dr. Henry B. Stephens, Memphis, aged 78, died November 3 of cerebral hemorrhage and arteriosclerosis.

Dr. Charles Elliott Ristline, Knoxville, aged 94, died January 10 of pneumonia.

Dr. J. A. Reynolds, Chattanooga, aged 47, died December 7.

TEXAS

The Dallas Southern Clinical Conference will be held in Dallas, March 11-14. For further information address the Secretary, Dr. George A. Schenewerk, Medical Arts Building, Dallas.

The Texas Association of Obstetricians and Gynecologists has elected the following officers for the coming year: President, Dr. H. Reid Robinson, Galveston; President-Elect, Dr. Roy L. Grogan, Fort Worth; Vice-President, Dr. Minnie L. Maffett, Dallas; Secretary-Treasurer, Dr. Julius McIver, Dallas.

Dr. Harold Wood, San Antonio, Assistant City Health Officer, is taking Public Health work at Johns Hopkins University.

Dr. Elbert Caldwell, Tyler, was recently appointed part-time physician to assist Dr. D. T. Bundy, County Health Officer, in operating the Smith County Syphilis Clinic.

Dr. John W. Spies, Galveston, recently attended a conference on Inter-American Relations in the field of education at Washington, on the invitation of Secretary of State Cordell Hull.

The Intercity Radiological Club, composed of radiologists of Dallas and Fort Worth, has elected the following officers for the coming year: President, Dr. J. M. Martin, Dallas; Vice-President, Dr. Palmer Wigby, Dallas; Secretary-Treasurer, Dr. E. V. Powell, Fort Worth.

The Big Bend Counties Medical Society has organized itself as a component unit of the State Medical Association of Texas, including Davis, Presidio, Brewster, Terrell and Pecos Counties, and elected the following officers for the coming year: President, Dr. Joseph C. Darracott, Marfa; Vice-President, Dr. J. Campbell Kern, Sanderson; Secretary-Treasurer, Dr. Joel Wright, Alpine.

Dr. John A. Wiggins, San Angelo, and Miss Jane Harper, Dallas, were married November 18, 1939.

Dr. W. W. Agnew has moved from Odessa to Fort Worth.

Dr. Raymond E. Baxter has moved from Wichita Falls to Bloomington, Illinois.

Dr. J. B. Birt has moved from Sanatorium to Harper.

Dr. Evan C. Bourdon has moved from Wills Point to Nashville, Tennessee.

Dr. R. M. Calder has moved from San Antonio to Baltimore, Maryland.

Dr. George B. Cornick has moved from San Antonio to San Angelo.

Dr. F. M. Dille has moved from Pleasanton to Greeley, Colorado.

Dr. U. J. Dowling has moved from Hamlin to Sweetwater.

Dr. James W. Eckhardt has moved from Yorktown to Austin.

Dr. A. B. Goldston has moved from Pampa to Amarillo.

Dr. Walter P. Kochmann has moved from Temple to Waco.

Dr. Walter A. Minsch has moved from Sanatorium to San Angelo.

Dr. Samuel Perlman has moved from Longview to Carthage.

Dr. W. F. Pickett has moved from Dallas to CCC Camp, Perryton.

Dr. Elsie G. Westley has moved from San Antonio to Fort Mills, Philippine Islands.

Deaths

Dr. Jules John Delambre, Houston, aged 61, died October 28 of coronary occlusion.

Dr. William Joseph Hutchinson, San Antonio, aged 73, died October 30 of tuberculosis.

Dr. Aaron D. Sanders, Corsicana, aged 68, died October 21 of cerebral hemorrhage and arteriosclerosis.

Dr. Richard H. Simpson, Dallas, aged 77, died October 29 of chronic nephritis.

Dr. Herbert Elmer Stevenson, El Paso, aged 68, died November 2.

Dr. Winfield Grant McDeed, Houston, aged 60, died November 30.

Dr. Nicholas Lee Dudley, Goose Creek, aged 73, died November 20 of coronary occlusion.

Dr. Alonzo Newell Callaway, Tyler, aged 63, died November 24.

Dr. Wil Turney Williams, Beaumont, aged 70, died November 30.

Dr. D. Richard Waddle, Greenville, aged 69, died November 2.

VIRGINIA

The Lynchburg Academy of Medicine has elected the following officers for the coming year: President, Dr. E. G. Scott; Vice-President, Dr. Powell Dillard; Secretary-Treasurer, Dr. C. E. Keefer, all of Lynchburg.

The Danville-Pittsylvania Academy of Medicine has elected the following officers for the coming year: President, Dr. W. B. Sanger; Vice-Presidents, Dr. M. H. Watson and Dr. W. E. Jennings; Secretary-Treasurer, Dr. E. E. Barksdale, all of Danville.

The Richmond Academy of Medicine has elected the following officers for the coming year: President, Dr. J. Powell Williams;

Continued on page 52

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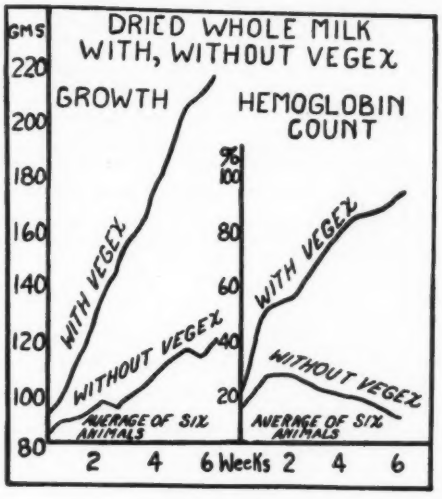

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Continued from page 50

President-Elect, Dr. William B. Porter; Vice-Presidents, Dr. E. H. Terrell and Dr. H. J. Warthen, all of Richmond.

The Fredericksburg Medical Society has elected the following officers for the coming year: President, Dr. L. Philip Cox, Fredericksburg; Vice-President, Dr. L. F. Lee, Passapatanzy; Secretary-Treasurer, Dr. William Butzner, Jr., Richmond.

Dr. W. D. Kendig, Kenbridge, was recently re-elected Chairman of the Lunenburg County Democratic Committee for 1940.

Dr. Wilbur R. Southwart, Richmond, of the Medical Corps, First Virginia Infantry, has been promoted to Major and assigned to duty with the Headquarters Second Battalion, a unit recently allocated to Virginia.

Dr. Frederick P. Barrlow, II, Portsmouth, of the Medical Corps, 111th Field Artillery, has been promoted to Major of the medical detachment.

Dr. William B. Wilkins, Alexandria, has moved to West Palm Beach, Florida.

Dr. S. Beverly Cary, Roanoke, announces the association of Dr. Frank Helvestine, Jr. They have offices in the Medical Arts Building and limit their practice to urology.

Deaths

Dr. Benjamin Franklin Nolan, Bassetts, aged 86, died October 20 of angina pectoris.

Dr. Austen Michklem, Rockfish, aged 81, died November 23 of coronary thrombosis.

Dr. Rudolph Angus Nichols, Jr., Richmond, aged 39, died December 10 following a heart attack.

Dr. Bertrand Ryland Hudnall, Covington, aged 64, died December 21 of a heart attack following pneumonia.

Dr. James Jett McCormick, Norfolk, aged 71, died December 21.

WEST VIRGINIA

The Barbour-Randolph-Tucker County Medical Society has elected the following officers for the coming year: President, Dr. Hu C. Myers, Philippi; Vice-Presidents, Dr. L. U. Lumpkin, Elkins, and Dr. S. J. Skar, Davis; Secretary-Treasurer, Dr. Guy H. Michael, Belington, re-elected.

The Cabell County Medical Society has elected the following officers for the coming year: President, Dr. W. F. Beckner; Vice-President, Dr. George Lyon; Treasurer, Dr. Frank Barker; Secretary, Dr. Jay L. Hutchinson, all of Huntington.

The Eastern Panhandle Medical Society has elected the following officers for the coming year: President, Dr. G. P. Morison, Charles Town; Vice-Presidents, Dr. W. L. Haltom, Martinsburg, and Dr. C. C. Johnson, Harpers Ferry; Secretary-Treasurer, Dr. M. H. Porterfield, Martinsburg, re-elected.

The Greenbrier Valley Medical Society has elected the following officers for the coming year: President, Dr. Guy Hinsdale, White Sulphur Springs; Vice-President, Dr. D. G. Preston, Lewisburg; Secretary-Treasurer, Dr. A. G. Lanham, Ronceverte.

The Hancock County Medical Society has elected the following officers for the coming year: President, Dr. Thomas H. Bruce, New Cumberland; Vice-President, Dr. A. Sunsweri, Weirton; Secretary-Treasurer, Dr. Godfrey L. Beaumont, New Cumberland.

The Harrison County Medical Society has elected the following officers for the coming year: President, Dr. George F. Evans; Vice-President, Dr. Creed C. Greer; Secretary, Dr. L. E. Neal; Treasurer, Dr. R. T. Humphries, all of Clarksburg.

The Logan County Medical Society has elected the following officers for the coming year: President, Dr. W. H. Parker, Braeholm; Vice-President, Dr. C. A. Davis, Logan; Secretary-Treasurer, Dr. J. W. Carney, Logan, re-elected.

The Mason County Medical Society has elected the following officers for the coming year: President, Dr. E. L. McElfresh, Point Pleasant; Vice-President, Dr. C. W. Petty, Hartford; Secretary-Treasurer, Dr. J. H. Toupkin, Point Pleasant.

The Monongalia County Medical Society has elected the following officers for the coming year: President, Dr. G. Ralph Maxwell; Vice-President, Dr. William B. Scherr; Secretary, Dr. Carl E. Johnson; Treasurer, Dr. L. W. Cobun, all of Morgantown.

The Academy of Medicine of Parkersburg has elected the following officers for the coming year: President, Dr. James L. Wade; Vice-President, Dr. Athey R. Lutz; Secretary-Treasurer, Dr. A. C. Woofter, re-elected, all of Parkersburg.

Deaths

Dr. George J. E. Sponseller, Martinsburg, aged 66, died November 12.

Dr. Edward Thomas Wetzel, West Union, aged 67, died November 4 of cerebral hemorrhage.

Dr. Thomas J. Conaway, Barrackville, aged 76, died November 7.

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1. Privatera, A. T., Arch. of Ped. April, 1938
2. Eddy, Walter E. (Special Research Report on Vi-Syneral).
3. Allen, A. M., Medical Record, April 19, 1939

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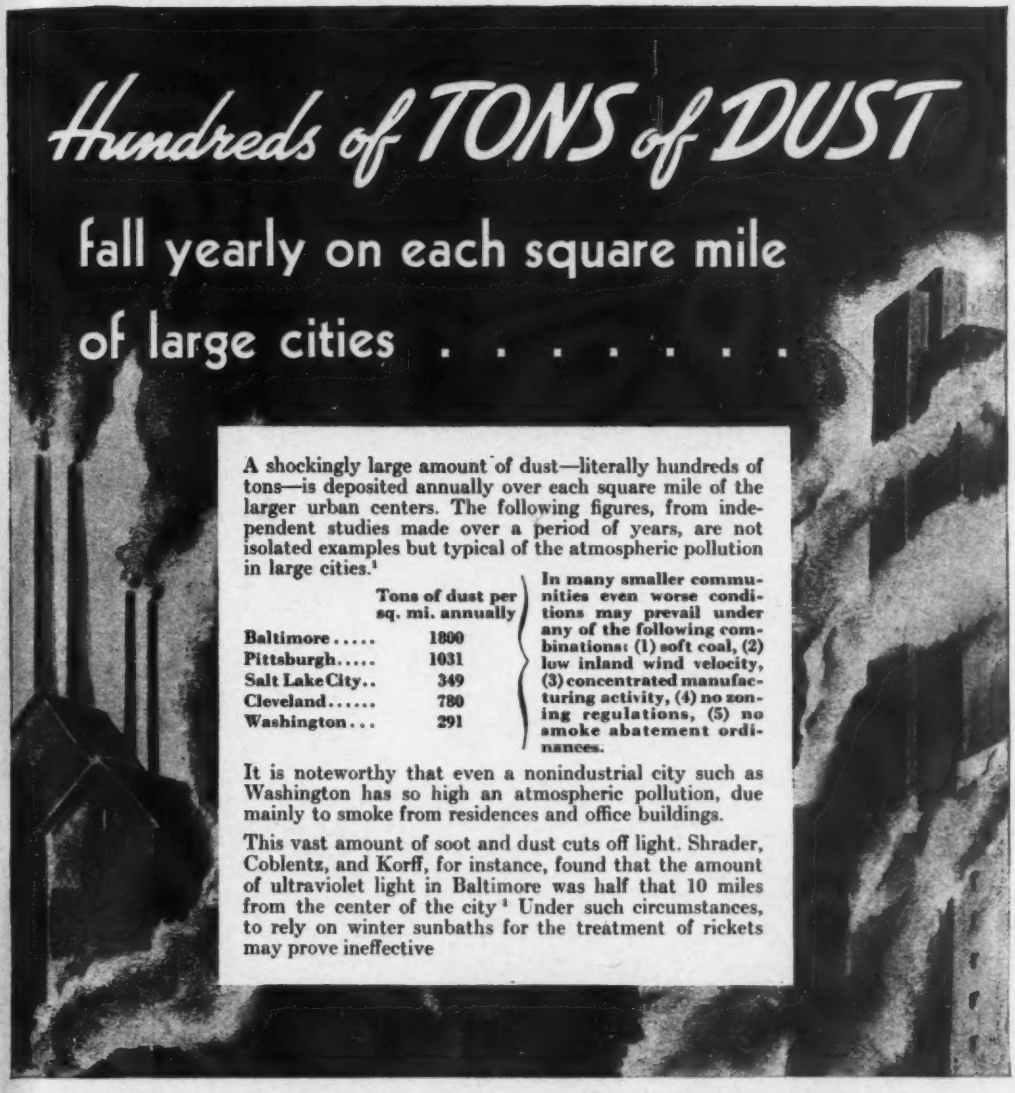

A shockingly large amount of dust—literally hundreds of tons—is deposited annually over each square mile of the larger urban centers. The following figures, from independent studies made over a period of years, are not isolated examples but typical of the atmospheric pollution in large cities.[1]

	Tons of dust per sq. mi. annually
Baltimore.....	1800
Pittsburgh.....	1031
Salt Lake City..	349
Cleveland.....	780
Washington...	291

In many smaller communities even worse conditions may prevail under any of the following combinations: (1) soft coal, (2) low inland wind velocity, (3) concentrated manufacturing activity, (4) no zoning regulations, (5) no smoke abatement ordinances.

It is noteworthy that even a nonindustrial city such as Washington has so high an atmospheric pollution, due mainly to smoke from residences and office buildings.

This vast amount of soot and dust cuts off light. Shrader, Coblentz, and Korff, for instance, found that the amount of ultraviolet light in Baltimore was half that 10 miles from the center of the city.[1] Under such circumstances, to rely on winter sunbaths for the treatment of rickets may prove ineffective

a dependable antiricketic
OLEUM PERCOMORPHUM

At a cost to the patient of less than 1 cent a day you can prescribe 1,000 vitamin D units of Oleum Percomorphum, a dose regarded as adequate for the prophylaxis of rickets. At no additional cost the patient receives at least 7,000 units of vitamin A. Each gram supplies not less than 60,000 vitamin A units and 8,500 vitamin D units (U.S.P.). This means that the time-tried benefits of cod liver oil without its necessarily large dose are available even to premature and young infants, who are often most in need of antiricketic therapy. Supplied in 10 and 50 c.c. bottles and 10-drop capsules (boxes of 25 and 100).

[1]U. S. Public Health Bulletin No. 224.

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